

Optimalizace léčebných strategií a význam vybraných prognostických faktorů u Hodgkinova lymfomu

Habilitační práce

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Abstract

Over the past four decades, advances in radiation therapy, the development of combination chemotherapy regimens, and the introduction of antibody-drug conjugates and immune checkpoint inhibitors have significantly increased cure rates in patients with Hodgkin lymphoma (HL). Nevertheless, numerous unresolved questions remain regarding its treatment. These primarily concern the minimization of late adverse effects—which is critical given that the majority of patients are under 35 years of age—and the identification of prognostic factors to detect patients at high risk of disease relapse.

Most patients with HL can be cured with standard therapy; long-term survival exceeds 90% in localized stages and reaches 70–80% in advanced stages. However, treatment based on chemotherapy and radiotherapy carries a risk of developing often severe late complications. Identifying risk factors thus allows for the optimization of therapy based on the expected clinical outcome, thereby preventing both overtreatment in some patients and undertreatment in others.

The original articles included and commented on in this habilitation thesis address these uncertainties in the field of treatment optimization and risk stratification in HL. All studies described herein were conducted with the goal of contributing to the development of strategies for effective therapy that achieve maximum treatment response while minimizing the risk of adverse effects.

The thesis comprises a total of 9 contributions. Initially, our research focused on the de-escalation of treatment intensity in localized and advanced stages of HL. Subsequently, we turned our attention to evaluating the efficacy of the CD30-targeted antibody-drug conjugate brentuximab vedotin. Furthermore, we investigated the prognostic significance of PD-L1 expression in newly diagnosed HL cases and the role of extranodal involvement. In subsequent studies, we focused on the incidence of secondary malignancies following HL treatment and the prognostic value of positron emission tomography (PET) performed prior to autologous stem cell transplantation in patients with relapsed disease.

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1 Úvod

I. Hodgkinův lymfom jako model moderní onkologické léčby.

Hodgkinův lymfom (HL) představuje jedno z nejlépe prostudovaných nádorových onemocnění a současně jeden z nejvýznamnějších příkladů pokroku moderní klinické onkologie. Přestože tvoří přibližně 10-15 % všech lymfomů a jeho incidence je ve srovnání s ostatními malignitami relativně nízká, stal se HL modelem, na kterém byly během posledních desetiletí ověřovány základní principy kombinované chemoterapie, radioterapie, multimodální léčby i individualizace léčebných postupů. Výsledky rozsáhlých mezinárodních klinických studií prokazují, že HL patří mezi maligní onemocnění s nejvyšší pravděpodobností dlouhodobého vyléčení. Současnými léčebnými postupy lze dosáhnout trvalé remise přibližně u 80–90 % nemocných, přičemž u pacientů s časnými stadii onemocnění přesahuje pravděpodobnost dlouhodobého přežití 90 %. ¹⁻³

Charakteristickým rysem tohoto onemocnění je jeho věkové rozložení s nejvyšší incidencí mezi 20. a 35. rokem života, tedy v období profesní, reprodukční i sociální aktivity nemocných. Vzhledem k dlouhé očekávané době přežití získává vedle samotné eradikace nádoru stále větší význam také kvalita života po ukončení léčby. U pacientů, kteří jsou po desetiletí považováni za vyléčené, mohou pozdní komplikace protinádorové léčby představovat významnou příčinu morbiditu i mortality. Mezi nejzávažnější patří sekundární malignity, kardiovaskulární onemocnění, plicní toxicita, endokrinní poruchy a poruchy fertility. Poznání významu těchto dlouhodobých následků vedlo k zásadní změně pohledu na léčebné cíle u HL. ⁴⁻⁸

Historický vývoj léčby HL lze charakterizovat jako postupný přechod od snahy dosáhnout maximální protinádorové účinnosti ke strategii usilující o optimální rovnováhu mezi účinností léčby a její dlouhodobou toxicitou. V prvních desetiletích rozvoje systémové léčby bylo hlavním cílem zvýšení podílu vyléčených nemocných prostřednictvím intenzifikace chemoterapie a radioterapie. Tento přístup vedl k dramatickému zlepšení dlouhodobých léčebných výsledků a představoval jeden z největších úspěchů klinické onkologie konce dvacátého století. S prodlužujícím se obdobím sledování se však postupně ukázalo, že dosažení dlouhodobé remise může být u části nemocných spojeno s významnou pozdní morbiditou a mortalitou související s předchozí léčbou HL. Dlouhodobé observační studie prokázaly, že pozdní

komplikace protinádorové terapie se mohou manifestovat i více než dvě až tři desetiletí po jejím ukončení a u části pacientů představují významnější příčinu úmrtí než samotný HL.⁴⁻¹⁰

Tyto poznatky vedly k zásadní proměně léčebné strategie. Úspěšnost léčby již není hodnocena pouze podle dosaženého přežití bez progrese nebo celkového přežití, ale stále více také podle dlouhodobé bezpečnosti léčby, kvality života a zachování orgánových funkcí. Současným cílem léčby proto není pouze maximalizace počtu vyléčených pacientů, ale především dosažení co nejvyšší pravděpodobnosti trvalého vyléčení při současné minimalizaci akutní i pozdní toxicity léčby.^{2,4-11}

V posledních letech došlo k dalšímu zásadnímu posunu. Pozornost se přesunula od jednotného přístupu ke všem nemocným směrem k individualizaci léčby podle biologických vlastností nádoru, rozsahu onemocnění a časné léčebné odpovědi.

Významnou roli v tomto procesu sehrálo zavedení pozitronové emisní tomografie s využitím ¹⁸F-fluorodeoxyglukózy kombinované s výpočetní tomografií (PET/CT), které přineslo možnost přesnějšího stanovení rozsahu onemocnění, hodnocení časné metabolické odpovědi na léčbu a přesnějšího posouzení reziduálních ložisek po jejím ukončení. Právě metabolická odpověď hodnocená pomocí PET/CT se postupně stala jedním z nejvýznamnějších prediktivních faktorů léčebného výsledku a vytvořila základ pro rozvoj PET-adaptovaných léčebných strategií.¹²⁻¹⁵

Současně s rozvojem zobrazovacích metod došlo k významnému prohloubení poznatků o biologii HL. Detailnější porozumění vzájemným interakcím mezi Hodgkinovými a Reedovými–Sternbergovými buňkami a nádorovým mikroprostředím, významu imunitních kontrolních mechanismů i genetických změn vedlo nejen k identifikaci nových prognostických biomarkerů, ale také k vývoji cílené léčby, zejména inhibitorů kontrolních bodů imunitní odpovědi (immune checkpoint inhibitors; ICI) a konjugovaných monoklonálních protilátek.¹⁶⁻¹⁹

Vývoj léčby HL představuje postupný přechod od standardizovaných léčebných schémat ke stále přesnějšímu přizpůsobení léčebných postupů individuálním charakteristikám pacienta a onemocnění. Tento posun umožnil zejména pokrok v zobrazovacích metodách, hlubší poznání biologických mechanismů onemocnění a rozvoj cílené léčby a imunoterapie. Tyto změny současně vytvořily odborný rámec pro výzkumné aktivity předkládané v této habilitační práci, zaměřené na optimalizaci léčebných strategií a identifikaci prognostických faktorů, které mohou přispět k další individualizaci léčby pacientů s HL.^{2,12-19}

II. Změna léčebného postupu u HL

Na základě výsledků rozsáhlých prospektivních randomizovaných studií, které systematicky hodnotily možnosti eskalace i deeskalace léčby u jednotlivých skupin pacientů, byla postupně opuštěna strategie maximalizace pravděpodobnosti vyléčení i za cenu vyšší akutní a pozdní toxicity. Současné léčebné postupy usilují o dosažení optimální rovnováhy mezi léčebnou účinností a dlouhodobou bezpečností.^{11,20,21}

Prvním významným krokem bylo zavedení rizikově adaptované léčby podle klinického stadia a přítomnosti nepříznivých prognostických faktorů. U pacientů s časnými příznivými stadii se ukázalo, že vysoké pravděpodobnosti dlouhodobého vyléčení lze dosáhnout i při méně intenzivní léčbě, zatímco u nemocných s pokročilým nebo časným nepříznivým onemocněním bylo nezbytné použít intenzivnější léčebné režimy. Tento přístup vytvořil základ moderní stratifikace pacientů podle rizika a umožnil první úpravy intenzity léčby.^{11,20,21}

Další zásadní změnu představovalo zavedení časného hodnocení metabolické odpovědi pomocí PET/CT. Již první prospektivní studie prokázaly, že negativní PET po úvodních cyklech chemoterapie je spojena s mimořádně příznivou prognózou, zatímco přetrvávající metabolická aktivita představuje jeden z nejsilnějších prediktorů relapsu nebo progresu onemocnění. Časná metabolická odpověď po úvodních cyklech chemoterapie tak poskytuje přesnější informaci o pravděpodobnosti dlouhodobého léčebného úspěchu než vstupní klinické prognostické faktory. Prognostická hodnota časného PET se stala základem současných PET-adaptovaných léčebných strategií, které umožňují léčbu během jejího průběhu individualizovat. U nemocných s časnou kompletní metabolickou odpovědí lze u vybraných skupin bezpečně snížit intenzitu

léčby, zatímco pacienti s přetrvávající metabolickou aktivitou mohou profitovat z její intenzifikace nebo změny léčebného postupu. Význam PET/CT však přesahuje samotné hodnocení léčebné odpovědi. Metabolické zobrazení se stalo nedílnou součástí vstupního stanovení rozsahu onemocnění, plánování radioterapie i hodnocení reziduálních ložisek po ukončení léčby. Standardizace hodnocení pomocí Deauville skóre a doporučení Luganské klasifikace významně přispěly ke sjednocení hodnocení léčebné odpovědi v klinických studiích i běžné klinické praxi.^{12-15,22-24}

Současně s rozvojem PET-adaptovaných strategií pokračoval vývoj systémové léčby. Lepší porozumění biologii HL vedlo k zavedení cílené léčby zaměřené proti antigenu CD30 a následně inhibitorů kontrolních bodů imunitní odpovědi (ICI). Tyto léčebné modalitty nejprve významně zlepšily výsledky léčby relapsu HL, včetně refrakterního HL, a následně byly úspěšně začleněny i do léčby první linie. Moderní léčebné algoritmy tak již nejsou založeny pouze na klinickém stadiu onemocnění, ale stále více zohledňují biologické charakteristiky nádoru, metabolickou odpověď a individuální riziko každého pacienta.²³⁻²⁵

HL se stal modelovým onemocněním, na kterém byly ověřeny principy adaptace léčby podle časně léčebné odpovědi, využití moderních zobrazovacích metod i integrace cílené a imunologické léčby do standardních léčebných postupů. Individualizace léčby se tak stala základním principem současné péče o nemocné s HL a současně vytvořila prostor pro hledání nových prognostických a prediktivních markerů, které umožní další zpřesnění léčebných strategií.^{15,22-25}

III. Individualizace léčby Hodgkinova lymfomu

Individualizace léčby HL vychází z předpokladu, že pacienti představují heterogenní skupinu s rozdílným biologickým chováním onemocnění, odlišnou pravděpodobností léčebné odpovědi i různým rizikem pozdních komplikací léčby. Jedním z cílů současného výzkumu je proto identifikace faktorů, které umožní přizpůsobit intenzitu léčby charakteristikám konkrétního nemocného.^{14,26,27}

Historicky byla stratifikace pacientů založena především na klinických charakteristikách onemocnění. Významným prognostickým modelem se stal International Prognostic Score (IPS), publikovaný Hasencleverem a Diehlem, který kombinuje sedm klinických a laboratorních parametrů a umožňuje odhad rizika léčebného selhání u nemocných s pokročilým HL. Přestože IPS představoval po mnoho let základní nástroj rizikové stratifikace, jeho diskriminační schopnost se se zlepšujícími léčebnými výsledky postupně snižovala. Moderní léčebné strategie proto vyžadují přesnější predikci individuální léčebné odpovědi.^{26,27}

Vedle již zmíněného časného hodnocení metabolické odpovědi pomocí PET/CT se v posledních letech soustřeďuje pozornost také na kvantitativní parametry metabolického zobrazení. Mezi nejvíce studované ukazatele patří zejména celkový metabolický nádorový objem (baseline metabolic tumor volume, bMTV), který odráží celkovou metabolicky aktivní nádorovou masu před zahájením léčby. Vyšší hodnota bMTV byla opakovaně spojena s kratším přežitím bez progresu onemocnění a horší celkovou prognózou jak u nově diagnostikovaných pacientů, tak u nemocných s relabovaným nebo refrakterním HL. Jednotná hraniční hodnota bMTV však dosud nebyla stanovena, neboť výsledky jednotlivých studií se liší v závislosti na

charakteristikách hodnocené populace a použité metodě segmentace. Kombinace vstupního bMTV s časnou metabolickou odpovědí představuje jednu z nejslibnějších cest další individualizace léčebných postupů.^{28,29}

Stále většího významu nabývají také biologické charakteristiky nádoru. Pokroky v molekulární biologii umožnily detailnější poznání genetických změn Hodgkinových a Reedových–Sternbergových (HRS) buněk i jejich interakcí s nádorovým mikroprostředím. Zvláštní pozornost je věnována expresi ligandů PD-L1 a PD-L2, jejíž zvýšení souvisí zejména s genetickými změnami v oblasti 9p24.1 a představuje jeden z klíčových mechanismů úniku nádorových buněk před imunitním dohledem. Tyto poznatky nejen přispívají k vysvětlení mimořádné účinnosti inhibitorů PD-1 u relabovaného HL, ale současně otevírají možnosti využití biologických markerů k predikci léčebné odpovědi.¹⁶⁻¹⁹

Přes významný pokrok však dosud neexistuje biomarker, který by s dostatečnou přesností umožnil individualizovat léčbu všech nemocných. Současné prognostické modely proto stále častěji kombinují klinické charakteristiky, metabolické zobrazovací parametry a biologické markery s cílem zpřesnit rizikovou stratifikaci pacientů. Identifikace nových faktorů ovlivňujících prognózu a léčebnou odpověď představuje jeden z hlavních směrů současného výzkumu HL a současně významnou součást výzkumných aktivit předkládaných v této habilitační práci.^{18,27-29}

IV. Nevyřešené otázky současné léčby Hodgkinova lymfomu

Hlavní výzvou současné léčby HL již není pouze další zvyšování celkové léčebné úspěšnosti, ale především přesnější identifikace pacientů, kteří mohou profitovat z méně intenzivní léčby, a naopak nemocných vyžadujících časnou intenzifikaci léčby nebo využití nových léčebných modalit. Výzkum se proto zaměřuje na optimalizaci léčebných strategií s cílem zachovat vysokou pravděpodobnost dlouhodobého vyléčení a současně snížit riziko pozdních komplikací léčby.^{11,15,20-25,31}

Jedním z nejdiskutovanějších témat zůstává možnost bezpečné deeskalace léčby u pacientů s příznivou prognózou. Prospektivní randomizované studie ukázaly, že u nemocných s negativním interim PET lze u vybraných skupin snížit intenzitu léčby chemoterapií nebo modifikovat rozsah radioterapie. Současně však upozornily, že přílišná redukce léčby může být spojena s mírným zvýšením rizika relapsu. Optimální rovnováha mezi léčebnou účinností a dlouhodobou toxicitou proto zůstává předmětem dalšího výzkumu.^{11,15,30,31}

Na opačném konci spektra stojí otázka intenzifikace léčby u pacientů s vysokým rizikem selhání. Eskalované chemoterapeutické režimy založené na BEACOPP (bleomycin, etoposid, doxorubicin, cyklofosfamid, vinkristin, prokarbazin a prednison) sice vedou u části nemocných ke snížení rizika relapsu, jsou ale spojeny s vyšší akutní i dlouhodobou toxicitou, včetně poruch fertility, hematologických komplikací a sekundárních malignit. Vývoj nových režimů, zejména BrECADD (brentuximab vedotin, etoposid, cyklofosfamid, doxorubicin, dakarbazin a dexamethason), představuje snahu zachovat vysokou protinádorovou účinnost při současném snížení léčbou podmíněné toxicity.^{21,24,32,33}

Významnou oblastí současného výzkumu představuje také hledání přesnějších

biomarkerů ovlivňujících prognózu a léčebnou odpověď. Přestože časná metabolická odpověď hodnocená pomocí PET/CT představuje jeden z nejsilnějších prediktorů léčebného výsledku, sama o sobě nedokáže plně vystihnout biologickou heterogenitu onemocnění. Velká pozornost je proto věnována kvantitativním parametrům PET/CT umožňující objektivněji charakterizovat metabolickou aktivitu a rozsah nádorového postižení, molekulárním charakteristikám nádoru, genetickým změnám a nádorovému mikroprostředí. Cílem je vytvořit komplexní model rizikové stratifikace umožňující skutečně individualizovaný výběr léčby.^{18,28,29}

Další zásadní otázkou je optimální začlenění cílené a imunologické léčby do jednotlivých linií terapie. Brentuximab vedotin a inhibitory PD-1 významně změnily léčbu relapsu HL a jejich účinnost byla následně potvrzena také v léčbě první linie pokročilých stádií HL. Dosud však není jednoznačně stanoveno, kteří pacienti z těchto postupů profitují nejvíce, jaká je optimální sekvence jednotlivých léčebných modalit ani jaké biomarkery by měly být využity při výběru léčby.^{18,23-25}

S rostoucím počtem dlouhodobě přežívajících pacientů nabývá na významu prevence sekundárních malignit, kardiovaskulárních komplikací, poruch fertility a dalších pozdních nežádoucích účinků. Při hodnocení léčebných výsledků je proto stále větší důraz kladen nejen na účinnost léčby, ale také na kvalitu života, zachování orgánových funkcí a její dlouhodobou bezpečnost. Tyto aspekty se stávají nedílnou součástí klinického výzkumu a jsou stále více zohledňovány také v mezinárodních léčebných doporučeních.^{6-9, 23-33}

V. Koncepce předložené habilitační práce

Předložená habilitační práce je založena na souboru původních vědeckých publikací zaměřených na různé aspekty diagnostiky, léčby a prognózy klasického HL. Přestože jednotlivé práce vznikaly v průběhu delšího časového období a zabývají se různými dílčími otázkami, spojuje je společný odborný cíl – přispět k dalšímu rozvoji individualizace léčby nemocných s HL prostřednictvím úpravy léčebných strategií a stanovením prognostických a prediktivních faktorů využitelných v běžné klinické praxi.

První část předloženého souboru tvoří publikace vzniklé v rámci spolupráce s Německou studijní skupinou pro Hodgkinův lymfom (German Hodgkin Study Group, GHSG). Studie, na kterých jsem se podílel, významně přispěly k optimalizaci léčby časných i pokročilých stadií HL a jejich výsledky se staly součástí mezinárodních léčebných doporučení. Účast na těchto projektech mi poskytla jedinečnou možnost podílet se na tvorbě léčebných standardů a současně přinesla zkušenosti, které se následně promítly do mé vlastní výzkumné činnosti.

Na mezinárodní klinické studie tematicky navazují původní práce zaměřené na identifikaci faktorů ovlivňujících prognózu nemocných. Tyto studie hodnotí význam metabolického zobrazení pomocí PET/CT, extranodálního postižení, exprese PD-L1 i dalších klinických a biologických parametrů. Jejich společným cílem je zpřesnit rizikovou stratifikaci nemocných a přispět k výběru optimální léčebné strategie pro jednotlivé pacienty.

Další publikace rozšiřuje pohled na dlouhodobé výsledky léčby HL a zaměřuje se na pozdní komplikace, zejména sekundární malignity, a význam dlouhodobého sledování nemocných. Výsledky práce ukazují, že hodnocení úspěšnosti léčby HL nelze omezit pouze na dosažení kompletní remise či prodloužení přežití, ale musí zohledňovat také dlouhodobou bezpečnost léčby, kvalitu života a riziko pozdních nežádoucích účinků.

2. Léčba časných stádií Hodgkinova lymfomu

Vývoj léčby časných stádií HL, zahrnujících klinická stadia I a II podle klasifikace Ann Arbor, představuje jeden z nejvýznamnějších příkladů postupné individualizace onkologické léčby. Na základě výsledků prospektivních randomizovaných klinických studií dosahuje v současnosti většina pacientů dlouhodobého celkového přežití přesahujícího 90 %. Hlavním cílem léčby proto již není pouze dosažení maximální pravděpodobnosti vyléčení, ale současně také minimalizace její akutní a zejména pozdní toxicity. Vývoj léčebných strategií proto postupně směřoval od rozsáhlých radioterapeutických polí a vyšších dávek záření k redukci rozsahu a dávky radioterapie, optimalizaci intenzity chemoterapie a následně k racionální deeskalaci léčby u nemocných s příznivou prognózou, zatímco u pacientů s vyšším rizikem relapsu je cílem zachování dostatečné léčebné intenzity.

V období před zavedením účinné systémové chemoterapie představovala základ léčby časných stádií HL radioterapie s rozšířeným ozařovacím polem (extended-field radiotherapy, EF-RT), která zahrnovala ozáření všech uzlinových oblastí na jedné, případně na obou stranách bránice.^{34,35} Přestože tento přístup umožňoval dosáhnout vysoké lokální kontroly onemocnění, dlouhodobé sledování prokázalo významný výskyt pozdních komplikací, zejména sekundárních malignit a kardiovaskulárních onemocnění, které se staly významnou příčinou pozdní mortality dlouhodobě přežívajících pacientů.^{36,37} Zavedení režimu ABVD (doxorubicin, bleomycin, vinblastin a dakarbazin) následně umožnilo kombinovat systémovou léčbu s radioterapií, snížit rozsah ozářených polí a významně omezit pozdní toxicitu při zachování vysoké léčebné účinnosti.^{38,39}

Prvním významným krokem k vytvoření současného standardu kombinované léčby byla studie Německé studijní skupiny pro Hodgkinův lymfom (GHSG) HD7. Jejím cílem bylo ověřit, zda přidání systémové chemoterapie ke standardní radioterapii zlepší léčebné výsledky u pacientů s časným příznivým HL. Studie prokázala, že kombinace dvou cyklů ABVD následovaných radioterapií významně snižuje riziko selhání léčby ve srovnání se samotnou radioterapií, aniž by vedla k nepřijatelnému zvýšení toxicity. Její výsledky podpořily přechod od samotné radioterapie ke kombinované modalitní léčbě, která se následně stala standardem léčby časných stádií HL.⁴⁰

Dalším důležitým krokem byla studie GHSG HD8, která se zaměřila na pacienty s časnými nepříznivými stádii HL. Cílem studie bylo ověřit, zda lze po úvodní chemoterapii nahradit rozsáhlé ozařování (EF-RT) cílenějším ozářením pouze původně postižených uzlinových oblastí (involved-field radiotherapy, IF-RT), aniž by byla snížena účinnost léčby. Studie prokázala srovnatelnou kontrolu onemocnění při současně nižší toxicitě IF-RT, čímž položila základy moderní radioterapie využívající menší ozařované objemy a významně přispěla ke snížení pozdních nežádoucích účinků léčby.⁴¹

Významným mezníkem ve vývoji léčby HL byla studie GHSG HD10, která zahrnula nemocné s časným Hodgkinovým lymfomem s příznivou prognózou, definovanou absencí rizikových faktorů, mezi něž patřily B-symptomy, zvýšená sedimentace erytrocytů, postižení tří a více lymfatických oblastí, extranodální postižení a objemné mediastinální postižení. Cílem studie bylo ověřit, zda lze u pacientů s příznivou prognózou bezpečně snížit intenzitu kombinované léčby, aniž by byla ohrožena její účinnost. Studie porovnávala standardní léčbu čtyřmi cykly režimu ABVD následovanými radioterapií v dávce 30 Gy s méně intenzivními léčebnými postupy využívajícími dva nebo čtyři cykly ABVD a radioterapii v dávce 20 nebo 30 Gy. Výsledky prokázaly, že léčba dvěma cykly ABVD následovanými radioterapií 20 Gy dosahuje stejné účinnosti jako intenzivnější léčebné režimy, přičemž je spojena s nižší akutní toxicitou. Studie HD10 tak jako první prospektivní randomizovaná studie fáze III poskytla přesvědčivé důkazy o možnosti bezpečné deeskalace kombinované léčby u pacientů s časným příznivým HL. Její výsledky vedly k přijetí režimu 2× ABVD následovaného radioterapií 20 Gy jako standardní léčby této skupiny nemocných v Evropě a následně významně ovlivnily i další mezinárodní doporučení.¹¹ Studie HD10 je dnes považována za jednu z klíčových studií, které položily základy moderní deeskalační strategie v léčbě HL a vytvořily východisko pro další klinické studie zaměřené na individualizaci léčby podle časně metabolické odpovědi.

Na výsledky studie HD10 navázala studie GHSG HD11, jejímž cílem bylo optimalizovat léčbu pacientů s časným nepříznivým HL a stanovit optimální intenzitu chemoterapie i dávku radioterapie. Studie prokázala, že čtyři cykly režimu ABVD následované radioterapií v dávce 30 Gy představují účinnou a bezpečnou léčebnou strategii, která se stala standardem léčby této skupiny pacientů v rámci GHSG a byla převzata do evropských doporučení.²⁰

Dalším významným krokem byla mezinárodní randomizovaná studie fáze III GHSG HD14, jejímž cílem bylo ověřit, zda lze u pacientů s časným nepříznivým HL dále zlepšit výsledky léčby krátkou intenzifikací úvodní chemoterapie. Studie porovnávala standardní léčbu čtyřmi cykly ABVD následovanými radioterapií s intenzifikovaným režimem sestávajícím ze dvou cyklů eskalovaného BEACOPP následovaných dvěma cykly ABVD a následnou radioterapií. Výsledky prokázaly, že krátká intenzifikace chemoterapie významně zlepšuje kontrolu onemocnění a prodlužuje přežití bez progresu při přijatelné toxicitě, aniž by vedla ke zvýšení léčebné mortality nebo výskytu sekundárních malignit. Studie HD14 tak jako první prokázala, že u pacientů s časným nepříznivým HL může krátká intenzifikace úvodní léčby významně zlepšit dlouhodobé léčebné výsledky. Její závěry vedly ke změně léčebné strategie GHSG a významně ovlivnily evropská doporučení pro léčbu této skupiny nemocných.⁴²

Další vývoj léčby lokalizovaných stadií HL byl spojen se zavedením PET/CT do hodnocení časně léčebné odpovědi. Tento přístup umožnil přejít od rozhodování založeného pouze na vstupních rizikových faktorech k individualizaci léčby podle metabolické odpovědi nádoru.

Jednou z prvních studií hodnotících tento přístup byla britská studie RAPID, jejímž cílem bylo ověřit, zda lze u pacientů s časným příznivým HL a negativním PET po úvodní chemoterapii bezpečně vynechat konsolidační radioterapii. Studie ukázala, že vynechání radioterapie je spojeno s mírně vyšším rizikem relapsu, avšak bez prokazatelného negativního dopadu na celkové přežití. Výsledky studie zdůraznily nutnost individuálně zvažovat přínos snížení pozdní toxicity oproti mírně vyššímu riziku relapsu³⁰

Obdobnou otázku řešila mezinárodní studie EORTC/LYSA/FIL H10, která hodnotila PET-adaptovanou léčbu u pacientů s časným příznivým i nepříznivým HL. Studie potvrdila, že vynechání radioterapie u PET-negativních pacientů vede ke zvýšení rizika relapsu, přestože celkové přežití zůstává vynikající. Výsledky studie tak podpořily zachování radioterapie jako standardní součásti léčby většiny pacientů s časnými stadii HL³¹

Na tuto problematiku navázala studie GHSG HD16, jejímž cílem bylo ověřit možnost vynechání radioterapie u pacientů s časným příznivým HL, kteří dosáhli negativního PET po dvou cyklech ABVD. Studie prokázala, že vynechání radioterapie vede ke zhoršení přežití bez progresu, a potvrdila tak význam kombinované léčby i u pacientů s negativní časnou metabolickou odpovědí⁴³

Odlišný přístup zvolila studie GHSG HD17, která hodnotila pacienty s časným nepříznivým HL léčené intenzifikovaným režimem 2× eskalovaný BEACOPP + 2× ABVD. Cílem studie bylo ověřit, zda lze u nemocných s negativním PET po ukončení chemoterapie bezpečně vynechat konsolidační radioterapii. Studie prokázala, že u pacientů s negativním PET lze radioterapii vynechat bez významného zhoršení léčebných výsledků, což představovalo další významný krok směrem k individualizaci léčby a omezení pozdní radiační toxicity.⁴⁴

Současná léčebná strategie časných stadií HL je založena na kombinaci účinné systémové léčby, moderních radioterapeutických technik a individualizaci léčby podle časně metabolické odpovědi hodnocené pomocí PET/CT. Vývoj radioterapie HL směřoval k postupnému zmenšování ozařovaných objemů, od EF-RT přes IF-RT až k moderním konceptům radioterapie postižených uzlin (IN-RT) a postižených oblastí (IS-RT), které umožňují omezit expozici okolních zdravých tkání při zachování účinné lokální kontroly onemocnění.⁴⁵ U vybraných pacientů, zejména s mediastinálním postižením, lze na základě individuálního porovnání ozařovacích plánů zvážit také protonovou radioterapii, která umožňuje snížit radiační zátěž srdce, plic a prsní tkáně.⁴⁶

Ve spolupráci s Německou studijní skupinou pro Hodgkinův lymfom (GHSG) jsme se podíleli na klinickém výzkumu zaměřeném na optimalizaci léčebných postupů u časných stadií HL. Redukce intenzity léčby u pacientů s příznivou prognózou a naopak její mírná intenzifikace u nemocných s nepříznivými prognostickými faktory vedly k velmi dobrým léčebným výsledkům a přispěly k vytvoření základů individualizovaného přístupu k léčbě časných stadií HL. Detailnější popis přináší následující publikace.

Engert A, Plütschow A, Eich HT, Lohri A, Dörken B, Borchmann P, Berger B, Greil R, Willborn KC, Wilhelm M, Debus J, Eble MJ, Sökler M, Ho A, Rank A, Ganser A, Trümper L, Bokemeyer C, Kirchner H, Schubert J, **Král Z**, Fuchs M, Müller-Hermelink HK, Müller RP, Diehl V. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med. 2010 Aug 12;363(7):640-52. doi: 10.1056/NEJMoa1000067. PMID: 20818855.

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ORIGINAL ARTICLE

Reduced Treatment Intensity in Patients with Early-Stage Hodgkin's Lymphoma

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ABSTRACT

BACKGROUND

Whether it is possible to reduce the intensity of treatment in early (stage I or II) Hodgkin's lymphoma with a favorable prognosis remains unclear. We therefore conducted a multicenter, randomized trial comparing four treatment groups consisting of a combination chemotherapy regimen of two different intensities followed by involved-field radiation therapy at two different dose levels.

METHODS

We randomly assigned 1370 patients with newly diagnosed early-stage Hodgkin's lymphoma with a favorable prognosis to one of four treatment groups: four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by 30 Gy of radiation therapy (group 1), four cycles of ABVD followed by 20 Gy of radiation therapy (group 2), two cycles of ABVD followed by 30 Gy of radiation therapy (group 3), or two cycles of ABVD followed by 20 Gy of radiation therapy (group 4). The primary end point was freedom from treatment failure; secondary end points included efficacy and toxicity of treatment.

RESULTS

The two chemotherapy regimens did not differ significantly with respect to freedom from treatment failure ($P=0.39$) or overall survival ($P=0.61$). At 5 years, the rates of freedom from treatment failure were 93.0% (95% confidence interval [CI], 90.5 to 94.8) with the four-cycle ABVD regimen and 91.1% (95% CI, 88.3 to 93.2) with the two-cycle regimen. When the effects of 20-Gy and 30-Gy doses of radiation therapy were compared, there were also no significant differences in freedom from treatment failure ($P=1.00$) or overall survival ($P=0.61$). Adverse events and acute toxic effects of treatment were most common in the patients who received four cycles of ABVD and 30 Gy of radiation therapy (group 1).

CONCLUSIONS

In patients with early-stage Hodgkin's lymphoma and a favorable prognosis, treatment with two cycles of ABVD followed by 20 Gy of involved-field radiation therapy is as effective as, and less toxic than, four cycles of ABVD followed by 30 Gy of involved-field radiation therapy. Long-term effects of these treatments have not yet been fully assessed. (Funded by the Deutsche Krebshilfe and the Swiss Federal Government; ClinicalTrials.gov number, NCT00265018.)

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*Additional investigators in the HD10 study are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org.

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RADIATION THERAPY WAS THE ORIGINAL mainstay of treatment for patients who had early-stage Hodgkin's lymphoma with a favorable prognosis. With the use of such techniques as extended-field radiation therapy and total lymphoid irradiation, more than 80% of patients with localized disease became long-term survivors. However, the relapse rate with radiation therapy alone ranged from 20 to 40%,¹⁻³ and extended-field radiation therapy and total lymphoid irradiation were associated with the occurrence of secondary solid tumors.⁴⁻⁸ The integration of a chemotherapy regimen consisting of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)⁹ with radiation therapy resulted in greater efficacy and allowed the radiation field and dose to be reduced, leading to widespread use of the combined approaches in patients with early-stage Hodgkin's lymphoma and a favorable prognosis.^{10,11} Four cycles of ABVD followed by 30 Gy of involved-field radiation therapy is now regarded as the standard of care by many groups.¹¹⁻¹⁴ The use of chemotherapy alone has been considered as a potential alternative approach but remains controversial.¹⁵⁻¹⁹

Whether the number of treatment cycles and the radiation dose can be reduced in patients with early-stage Hodgkin's lymphoma and a favorable prognosis remains unclear. In an attempt to reduce the toxic effects of treatment while retaining full control of the cancer, the German Hodgkin Study Group (GHSG) in 1998 initiated a prospective, randomized, multicenter study (HD10) in which four cycles of ABVD chemotherapy were compared with two cycles of ABVD, and 30 Gy of involved-field radiation therapy was compared with 20 Gy of involved-field radiation therapy in patients receiving either of the two chemotherapy regimens.

METHODS

STUDY PATIENTS

We enrolled patients who had newly diagnosed Hodgkin's lymphoma in clinical stage I or II, as confirmed on histologic examination, with no clinical risk factors. Patients were eligible if they were between 16 and 75 years of age, had not been treated previously for Hodgkin's lymphoma, and were free of concurrent disease. (Details regarding the definitions of clinical risk factors and full descriptions of the inclusion and exclusion criteria are provided in the Supplementary Ap-

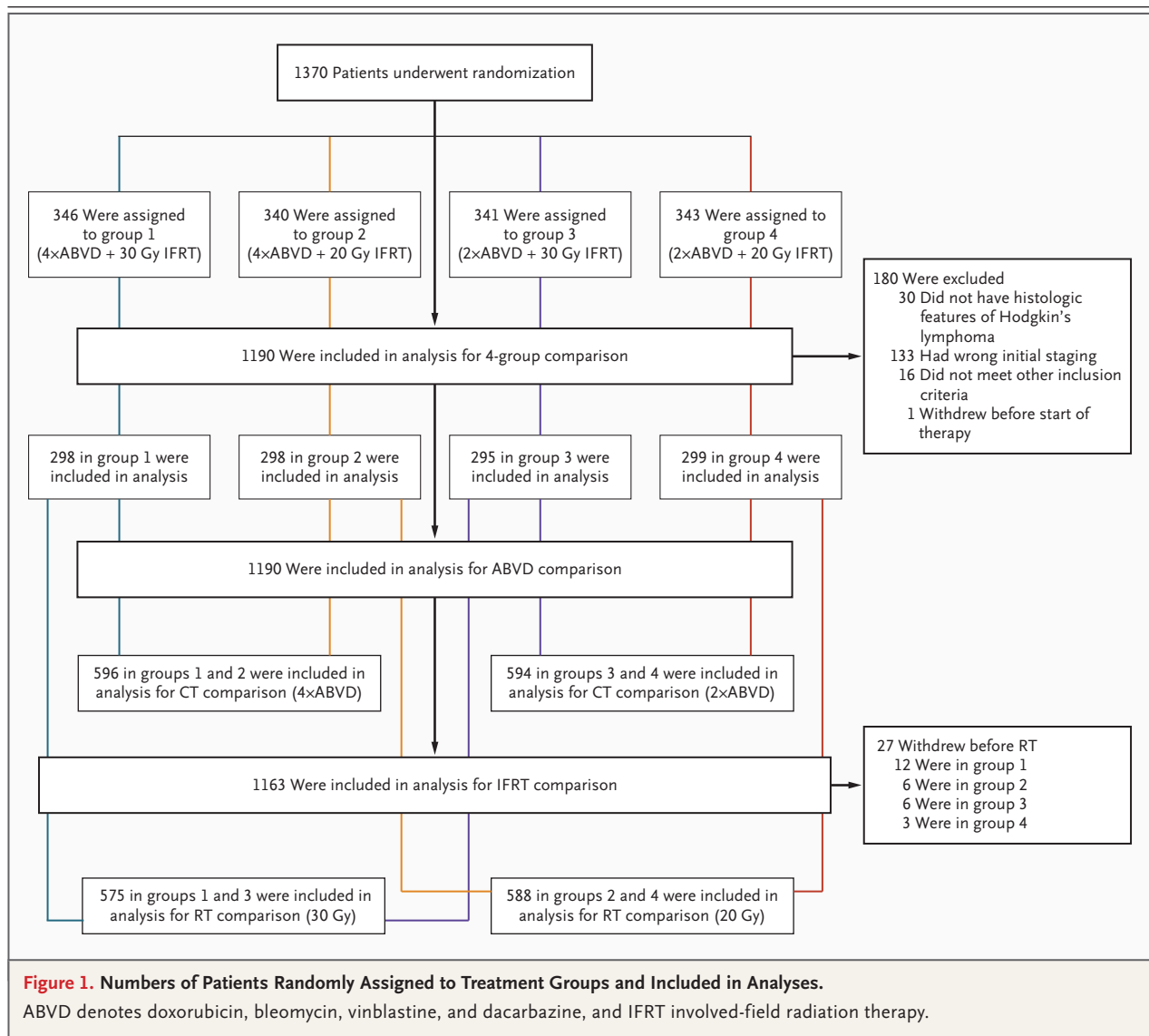
pendix, available with the full text of this article at NEJM.org.)

STUDY DESIGN

HD10 was a multicenter, randomized study of four different treatment regimens in patients with early-stage Hodgkin's lymphoma and a favorable diagnosis. Patients were recruited and treated at 329 hospitals and outpatient practices in Germany, Switzerland, the Netherlands, the Czech Republic, and Austria. After clinical staging had been completed and written informed consent obtained, patients were registered at the GHSG central trial office by telephone and then randomly assigned in a 1:1:1:1 ratio to one of four treatment groups: group 1 received four cycles of ABVD followed by 30 Gy of involved-field radiation therapy; group 2 received four cycles of ABVD followed by 20 Gy of involved-field radiation therapy; group 3 received two cycles of ABVD followed by 30 Gy of involved-field radiation therapy; and group 4 received two cycles of ABVD followed by 20 Gy of involved-field radiation therapy.

Stratification factors included trial center and prognostic factors that might influence the primary end point, such as age (<50 vs. ≥50 years), systemic symptoms, supradiaphragmatic or infradiaphragmatic disease, and albumin level (<4 vs. ≥4 g per deciliter). A 2-by-2 factorial design was chosen: for the chemotherapy comparison, the results in groups 1 and 2, which received four cycles of ABVD, were pooled, as were the results in groups 3 and 4, which received two cycles of ABVD. Similarly, for the radiation therapy comparison, the results in groups 1 and 3, which received the 30-Gy dose of involved-field radiation therapy, were pooled and compared with the results in groups 2 and 4, which received the 20-Gy dose of involved-field radiation therapy.

The HD10 protocol was designed by the GHSG steering committee and approved by the ethics committees of the participating centers. The study was performed in accordance with the protocol. An independent data and safety monitoring committee monitored the patients' safety and the efficacy of treatment throughout the 5-year study period. The GHSG central trial office was responsible for data collection, data management, and statistical analyses, as well as for internal presentations of results to the GHSG chairman and participating centers. The GHSG steering committee and chair decided to submit the results of the final analysis for publication. All authors contrib-



uted to the interpretation of the results and vouch for the accuracy and completeness of the data. The GHSG chair wrote the first draft of the manuscript and was supported by the lead statistician. There was no commercial involvement in this study and no financial support from industry.

CHEMOTHERAPY

ABVD was administered on days 1 and 15 in monthly cycles, at the following standard doses: doxorubicin, 25 mg per square meter of body-surface area; bleomycin, 10 mg per square meter; vinblastine, 6 mg per square meter; and dacarbazine, 375 mg per square meter. If the white-cell count was less than 2500 per cubic millimeter or

the platelet count was less than 80,000 per cubic millimeter on a day when chemotherapy was scheduled to be administered, treatment was postponed until normal levels were achieved. Granulocyte colony-stimulating factor was given if clinically indicated.

RADIATION THERAPY

Before treatment, all sites of disease were defined and documented by the treating medical oncologist and radiation oncologist. A central panel of experts in radiation oncology then planned involved-field radiation therapy as defined in the study protocol according to treatment group and, if necessary, revised the initial staging. The rec-

Table 1. Baseline Characteristics of the Patients According to Treatment Group.*									
Characteristic	Treatment Group†					Chemotherapy Comparison		Radiation Therapy Comparison	
	All Patients (N=1190)	Group 1: 4×ABVD + 30 Gy IFRT (N=298)	Group 2: 4×ABVD + 20 Gy IFRT (N=298)	Group 3: 2×ABVD + 30 Gy IFRT (N=295)	Group 4: 2×ABVD + 20 Gy IFRT (N=299)	Groups 1 and 2 (N=596)	Groups 3 and 4 (N=594)	Groups 1 and 3 (N=575)	Groups 2 and 4 (N=588)
Age — yr	38.8±14.3	39.5±14.2	38.6±14.5	38.3±14.3	38.7±14.4	39.0±14.3	38.5±14.3	38.6±13.9	38.6±14.4
Female sex — no. (%)	465 (39.1)	116 (38.9)	121 (40.6)	106 (35.9)	122 (40.8)	236 (39.6)	228 (38.4)	215 (37.4)	239 (40.6)
Ann Arbor stage — no. (%)‡									
IA	361 (30.3)	94 (31.5)	92 (30.9)	99 (33.6)	76 (25.4)	186 (31.2)	175 (29.5)	188 (32.7)	166 (28.2)
IB	24 (2.0)	5 (1.7)	6 (2.0)	7 (2.4)	6 (2.0)	11 (1.8)	13 (2.2)	12 (2.1)	12 (2.0)
IIA	738 (62.0)	182 (61.1)	184 (61.7)	175 (59.3)	197 (65.9)	366 (61.4)	372 (62.6)	346 (60.2)	375 (63.8)
IIB	66 (5.5)	17 (5.7)	15 (5.0)	14 (4.7)	20 (6.7)	32 (5.4)	34 (5.7)	29 (5.0)	35 (6.0)
Infradiaphragmatic disease — no. (%)	97 (8.2)	25 (8.4)	26 (8.7)	21 (7.1)	25 (8.4)	50 (8.4)	46 (7.7)	44 (7.7)	49 (8.3)
Histologic type of Hodgkin's lymphoma — no. of patients/total no. (%)§									
Nodular lymphocyte- predominant	81/1080 (7.5)	20/273 (7.3)	17/263 (6.5)	24/272 (8.8)	20/272 (7.4)	37/535 (6.9)	44/544 (8.1)	43/528 (8.1)	35/526 (6.7)
Lymphocyte-rich classic	98/1080 (9.1)	23/273 (8.4)	19/263 (7.2)	35/272 (12.9)	21/272 (7.7)	42/535 (7.9)	56/544 (10.3)	58/528 (11.0)	40/526 (7.6)
Nodular sclerosing	420/1080 (38.9)	101/273 (37.0)	112/263 (42.6)	98/272 (36.0)	109/272 (40.1)	213/535 (39.8)	207/544 (38.1)	197/528 (37.3)	219/526 (41.6)
Mixed cellularity	435/1080 (40.3)	118/273 (43.2)	103/263 (39.2)	99/272 (36.4)	115/272 (42.3)	220/535 (41.1)	214/544 (39.3)	206/528 (39.0)	213/526 (40.5)
Lymphocyte-depleted	1/1080 (0.1)	0	0	1/272 (0.4)	0	0	1/544 (0.2)	1/528 (0.2)	0
Not classified	45/1080 (4.2)	11/273 (4.0)	12/263 (4.6)	15/272 (5.5)	7/272 (2.6)	23/535 (4.3)	22/544 (4.0)	23/528 (4.4)	19/526 (3.6)

* Plus-minus signs are means ±SD. ABVD denotes doxorubicin, bleomycin, vinblastine, and dacarbazine, and IFR involved-field radiation therapy.

† These groups include all eligible patients.

‡ Information on stage of disease was missing for 1 patient in group 2.

§ Information on histologic subtype was available for 1080 patients (90.7%).

Table 2. Adverse Events According to Treatment Group.				
Event	Treatment Group*		Chemotherapy Comparison	
	Group 1: 4×ABVD + 30 Gy IFRT (N = 298)	Group 2: 4×ABVD + 20 Gy IFRT (N = 298)	Group 3: 2×ABVD + 30 Gy IFRT (N = 295)	Group 4: 2×ABVD + 20 Gy IFRT (N = 299)
	number of patients (percent)		no. of patients/total no. (%)	
Acute toxicity (grade III or IV)†				
At least one event			304/588 (51.7)	194/585 (33.2)
Anemia			7/588 (1.2)	1/585 (0.2)
Thrombopenia			3/588 (0.5)	0
Leukopenia			138/588 (23.5)	87/585 (14.9)
Nausea or vomiting			79/588 (13.4)	51/585 (8.7)
Mucositis			7/588 (1.2)	2/585 (0.3)
Gastrointestinal tract disorder or dysphagia			11/588 (1.9)	6/585 (1.0)
Respiratory tract disorder			12/588 (2.0)	2/585 (0.3)
Hair loss			165/588 (28.1)	89/585 (15.2)
Infection			30/588 (5.1)	10/585 (1.7)
Pain			9/588 (1.5)	14/585 (2.4)
Nervous system disorder			12/588 (2.0)	7/585 (1.2)
Secondary neoplasia‡				
Total	17 (5.7)	10 (3.4)	14 (4.7)	14 (4.7)
Acute myelocytic leukemia or myelodysplastic syndrome	2 (0.7)	0	0	0
Non-Hodgkin's lymphoma	4 (1.3)	3 (1.0)	3 (1.0)	5 (1.7)
Solid tumor	11 (3.7)	7 (2.3)	11 (3.7)	9 (3.0)
			18 (3.0)	20 (3.4)
			7 (1.2)	8 (1.3)
			22 (3.8)	16 (2.7)
			31 (5.4)	24 (4.1)
			2 (0.3)	0
			3/528 (0.6)	1/553 (0.2)
			2/528 (0.4)	0
			6/528 (1.1)	3/553 (0.5)
			1/528 (0.2)	0
			3/528 (0.6)	1/553 (0.2)
			2/528 (0.4)	0
			6/528 (1.1)	3/553 (0.5)
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			3/528 (0.6)	1/553 (0.2)
			2/528 (0.4)	0
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			6/528 (1.1)	3/553 (0.5)
			1/528 (0.2)	0
			3/528 (0.6)	1/553 (0.2)
			2/528 (0.4)	0

Death†	15 (5.0)	13 (4.4)	16 (5.4)	13 (4.3)	28 (4.7)	29 (4.9)	25 (4.3)	22 (3.7)
Total no. of deaths								
Cause of death								
Hodgkin's lymphoma	3 (1.0)	2 (0.7)	3 (1.0)	2 (0.7)	5 (0.8)	5 (0.8)	5 (0.9)	3 (0.5)
Toxicity of primary therapy	3 (1.0)	3 (1.0)	1 (0.3)	0	6 (1.0)§	1 (0.2)§	1 (0.2)	0
Toxicity of salvage therapy	0	0	4 (1.4)	1 (0.3)	0	5 (0.8)	3 (0.5)	0
Secondary neoplasia	3 (1.0)	0	5 (1.7)	3 (1.0)	3 (0.5)	8 (1.3)	8 (1.4)	3 (0.5)
Cardiovascular disorder	3 (1.0)	3 (1.0)	0	3 (1.0)	6 (1.0)	3 (0.5)	3 (0.5)	6 (1.0)

* These groups include all eligible patients.

† Information on the toxicity of primary chemotherapy (World Health Organization grade III or IV) was available for 1173 of 1190 patients (98.6%). Information on the toxicity of primary involved-field radiation therapy (IFRT) (Common Toxicity Criteria grade III or IV) was available for 1081 of 1163 patients (92.9%).

‡ A total of 57 of 1190 patients died (4.8%), and 55 of 1190 patients had a secondary neoplasm (4.6%). Median observation times were 91 months for overall survival and 79 months for freedom from treatment failure and progression-free survival; 884 patients (74.3%) were followed for at least 5 years after the end of therapy.

§ Causes of treatment-related deaths were pulmonary fibrosis, probably bleomycin-induced (in two patients assigned to four cycles of ABVD and one assigned to two cycles); sepsis (in two patients assigned to four cycles of ABVD); pneumonia (in one patient assigned to four cycles of ABVD); and not specified (in one patient assigned to four cycles of ABVD).

ommended interval between completion of the ABVD regimen and the start of radiation therapy was 4 to 6 weeks. Patients received either 30 Gy or 20 Gy of involved-field radiation therapy in single fractions of 1.8 to 2.0 Gy administered five times weekly.

STUDY END POINTS

The primary efficacy end point was freedom from treatment failure. Overall survival, progression-free survival, complete response, and treatment toxicity were secondary end points. Definitions of the study end points are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Proof of the noninferiority of the less intensive treatment, as compared with the standard treatment of four cycles of ABVD plus 30 Gy of involved-field radiation therapy, with respect to freedom from treatment failure at 5 years was the goal for both chemotherapy and radiation therapy. The noninferiority margin was defined as 7% in the study protocol. This led to the following two hypotheses: for chemotherapy, the 5-year rate of freedom from treatment failure in the two pooled groups assigned to two cycles of ABVD would be less than 7% below the rate in the two pooled groups assigned to four cycles, and for radiation therapy, the 5-year rate of freedom from treatment failure in the two pooled groups assigned to 20 Gy of involved-field radiation therapy would be less than 7% below the rate in the two pooled groups assigned to 30 Gy.

Survival rates for the four groups were compared with the use of the Kaplan-Meier method as well as stratified Cox regression analyses for hazard ratios (i.e., the chemotherapy comparison was stratified according to the radiation therapy assignment and vice versa), whereas outcomes and toxicity rates were compared with the use of Fisher's exact test. Tests of the hypotheses were performed according to the intention-to-treat principle and also on the basis of the treatment actually received. Subgroup analyses were not prespecified in the statistical-analysis plan, but we performed post hoc sensitivity analyses that excluded patients with nodular lymphocyte-predominant Hodgkin's lymphoma. The results of these sensitivity analyses are presented in the Supplementary Appendix.

In addition, to estimate the combined effect of reduced chemotherapy and reduced radiation therapy, we compared group 1, which received the most intensive therapy, with group 4, which received the

least intensive therapy. To detect a possible influence of prognostic factors or interactions between the effects of chemotherapy and those of radiation therapy, multivariate Cox regression analyses were specified in the protocol and performed as sensitivity analyses on the same data sets for comparing the two chemotherapy regimens and the two radiation therapy regimens.

RESULTS

PATIENTS

From May 1998 through January 2003, a total of 1370 patients were recruited and randomly assigned to treatment centrally. A total of 180 patients were excluded from all analyses: 30 because the reference histologic findings did not confirm Hodgkin's lymphoma, 133 because of incorrect initial staging, 16 because they did not meet other inclusion criteria, and 1 who met the inclusion criteria but could not subsequently be contacted (Fig. 1).

The baseline characteristics of the study patients are shown in Table 1. No significant differences were noted among the treatment groups for any of the characteristics shown. The median age of patients at randomization was 36 years (range, 16 to 75), and 61.0% were male; 30.3% had stage IA disease, 2.0% had stage IB, 62.0% had stage IIA, and 5.5% had stage IIB. (Information on stage of disease was missing for one patient in group 2.) The most frequent subtype diagnosed by the pathology reference panel was mixed cellularity (40.2%), and 8.1% of patients had infradiaphragmatic disease.

The main (intention-to-treat) analysis set for the initial chemotherapy comparison (CT1) comprised 1190 patients: 596 patients were randomly assigned to four cycles of ABVD and 594 to two cycles. Of these patients, 36 changed chemotherapy group or had major protocol violations; chemotherapy was not documented for 10 patients. The per-protocol analysis set for the chemotherapy comparison (CT2) therefore comprised 1144 patients (571 randomly assigned to four cycles of ABVD and 573 to two cycles). The main (intention-to-treat) analysis set for the radiation therapy comparison (RT1) included 1163 patients: 575 patients were randomly assigned to 30 Gy of involved-field radiation therapy and 588 to 20 Gy of involved-field radiation therapy. Of these pa-

tients, 33 had a change in the radiation therapy dose or had major protocol violations; radiation therapy documentation was missing for 17 patients. The per-protocol analysis set for the radiation therapy comparison included 1113 patients (557 in the 30-Gy groups and 556 in the 20-Gy groups). There were more protocol violations and group changes in the groups that received 20 Gy of involved-field radiation therapy than in those that received 30 Gy ($P=0.05$). However, since the per protocol analysis and the intention-to-treat analysis had similar results, these imbalances did not affect the final conclusions.

ADVERSE EVENTS

Toxicity of Treatment

Acute toxicity during chemotherapy was more frequent in patients who received four cycles of ABVD than in those who received two cycles (Table 2). Overall, 51.7% of the patients who received four cycles of ABVD had at least one instance of severe toxicity (grade III or IV) as compared with 33.2% of those who received two cycles ($P<0.001$). The most frequent events were hair loss (in 28.1% of patients receiving four cycles vs. 15.2% of those receiving two cycles) and hematologic toxic effects (24.0% vs. 15.0%). Infections were also more common with four cycles of ABVD than with two cycles (5.1% vs. 1.7%). Treatment-related deaths occurred in six patients treated with four cycles of ABVD (two died from pulmonary fibrosis, two from sepsis, one from pneumonia, and one from an unspecified cause) and in one patient treated with two cycles (from pulmonary fibrosis).

Severe toxicity (grade III or IV) was observed more often among the patients treated with 30 Gy of involved-field radiation therapy than among those who received 20 Gy (8.7% vs. 2.9%, $P<0.001$).

Secondary Neoplasia

Over a median follow-up period of 7.5 years (90 months), secondary cancers were diagnosed in a total of 55 patients (4.6%): 38 solid tumors, 15 cases of non-Hodgkin's lymphoma, and 2 cases of acute myeloid leukemia. There were no significant differences in the occurrence of secondary cancers among the four treatment groups ($P=0.59$), the pooled chemotherapy groups ($P=0.89$), or the pooled radiation therapy groups ($P=0.34$).

Table 3. Efficacy Outcomes According to Treatment Group.								
Outcome	Treatment Group				Chemotherapy Comparison		Radiation Therapy Comparison	
	Group 1: 4×ABVD + 30 Gy IFRT (N=298)	Group 2: 4×ABVD + 20 Gy IFRT (N=298)	Group 3: 2×ABVD + 30 Gy IFRT (N=295)	Group 4: 2×ABVD + 20 Gy IFRT (N=299)	Groups 1 and 2 (N=596)	Groups 3 and 4 (N=594)	Groups 1 and 3 (N=575)	Groups 2 and 4 (N=588)
Response — no. of patients (%) [*]								
Complete remission with or without residual radiologic abnormalities	287 (96.3)	288 (96.6)	287 (97.3)	288 (96.3)	575 (96.5)	575 (96.8)	569 (99.0)	573 (97.4)
Partial remission	2 (0.7)	2 (0.7)	3 (1.0)	1 (0.3)	4 (0.7)	4 (0.7)	4 (0.7)	3 (0.5)
No change	1 (0.3)	0	0	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Progression	0	1 (0.3)	3 (1.0)	2 (0.7)	1 (0.2)	5 (0.8)	0	1 (0.2)
Unknown	8 (2.7)	7 (2.3)	2 (0.7)	7 (2.3)	15 (2.5)	9 (1.5)	1 (0.2)	10 (1.7)
First relapse [†]	15 (5.0)	16 (5.4)	21 (7.1)	19 (6.4)	31 (5.2)	40 (6.7)	34 (5.9)	35 (6.0)
Survival rate — % (95% CI) [‡]								
At 5 years								
Overall survival	96.9 (94.2–98.4)	97.3 (94.6–98.6)	96.6 (93.7–98.1)	96.6 (93.7–98.1)	97.1 (95.4–98.2)	96.6 (94.7–97.8)	97.7 (96.1–98.7)	97.5 (95.9–98.5)
Freedom from treatment failure	92.8 (89.1–95.3)	93.1 (89.4–95.5)	90.9 (86.8–93.8)	91.2 (87.1–94.1)	93.0 (90.5–94.8)	91.1 (88.3–93.2)	93.4 (91.0–95.2)	92.9 (90.4–94.8)
Progression-free survival	93.9 (90.3–96.2)	93.2 (89.5–95.6)	90.8 (86.7–93.7)	91.6 (87.6–94.4)	93.5 (91.1–95.3)	91.2 (88.5–93.4)	93.7 (91.3–95.5)	93.2 (90.6–95.0)
At 8 years								
Overall survival	94.4 (90.2–96.8)	94.7 (90.9–97.0)	93.6 (89.6–96.1)	95.1 (91.7–97.2)	94.6 (92.0–96.4)	94.4 (91.9–96.1)	94.9 (92.2–96.6)	95.6 (93.2–97.1)
Freedom from treatment failure	87.2 (81.3–91.4)	89.9 (85.2–93.1)	85.5 (79.5–89.8)	85.9 (80.2–90.1)	88.4 (84.8–91.3)	85.7 (81.8–88.9)	87.8 (83.8–90.9)	88.6 (85.1–91.3)
Progression-free survival	88.4 (82.6–92.4)	90.0 (85.4–93.2)	85.4 (79.4–89.8)	86.5 (80.9–90.6)	89.1 (85.5–91.8)	86.0 (82.1–89.1)	88.1 (84.1–91.2)	88.9 (85.4–91.6)

* The final response is generally defined as the status of Hodgkin's lymphoma at the time of final restaging, 4 to 6 weeks after the patient has completed radiation therapy; if the patient does not have a complete remission, no further treatment is given, and there is no progression of disease within 6 months, the final response is retrospectively redefined as complete remission with residual radiologic abnormalities. CI denotes confidence interval.

† There were 6 cases of progression and 71 first relapses; 3 patients had 2 relapses each, and 1 patient had 3 relapses.

‡ Median observation times were 91 months for overall survival and 79 months for freedom from treatment failure and progression-free survival; 884 patients (74.3%) were followed for at least 5 years after the end of therapy.

Deaths

A total of 57 patients (4.8%) died during the follow-up period. The most frequent causes of death were secondary neoplasia (in 11), Hodgkin's lymphoma (in 10), cardiovascular events (in 9), toxicity of primary therapy (in 7), and toxicity of salvage therapy (in 5, all after having received two cycles of ABVD). No difference in mortality was noted among the four groups or between the combined chemotherapy groups and the combined radiation therapy groups (Table 2).

DISEASE CONTROL AND SURVIVAL

Final treatment outcomes were as follows: 1150 of 1190 patients (96.6%) had a complete remission, 8 (0.7%) had a partial remission, and 8 (0.7%) did not have a response (2 had no change and 6 had progression of disease during treatment). (Response criteria are described in the Supplementary Appendix.) For 24 patients (2.0%), the treatment outcome was unclear. The relapse rate was 6.0% (71 of 1190 patients). No significant differences were seen in rates of remission, progression, or relapse among the four treatment groups or between the combined chemotherapy groups and the combined radiation therapy groups.

The rates of freedom from treatment failure in the whole intention-to-treat analysis set of 1190 patients were estimated to be 92.0% (95% confidence interval [CI], 90.2 to 93.5) at 5 years and 87.1% (95% CI, 84.5 to 89.3) at 8 years. The overall survival rates for all 1190 patients were estimated to be 96.8% (95% CI, 95.7 to 97.7) at 5 years and 94.5% (95% CI, 92.8 to 95.8) at 8 years (Table 3). For the same patients, the rate of progression-free survival was estimated to be 92.4% (95% CI, 90.6 to 93.8) at 5 years and 87.6% (95% CI, 85.0 to 89.7) at 8 years.

CHEMOTHERAPY COMPARISON

In the intention-to-treat analysis, the median observation time for the primary end point, freedom from treatment failure, was identical in the two chemotherapy groups (79 months). The rate of freedom from treatment failure at 5 years was 93.0% with four cycles of ABVD (95% CI, 90.5 to 94.8) and 91.1% with two cycles (95% CI, 88.3 to 93.2) (Table 3). On the basis of the stratified Cox regression analysis, the hazard ratio for treatment failure with two cycles of ABVD as compared with four cycles was 1.17 (95% CI, 0.82 to 1.67). The 5-year estimated group difference (two cycles vs. four cycles) was -1.9 percentage points

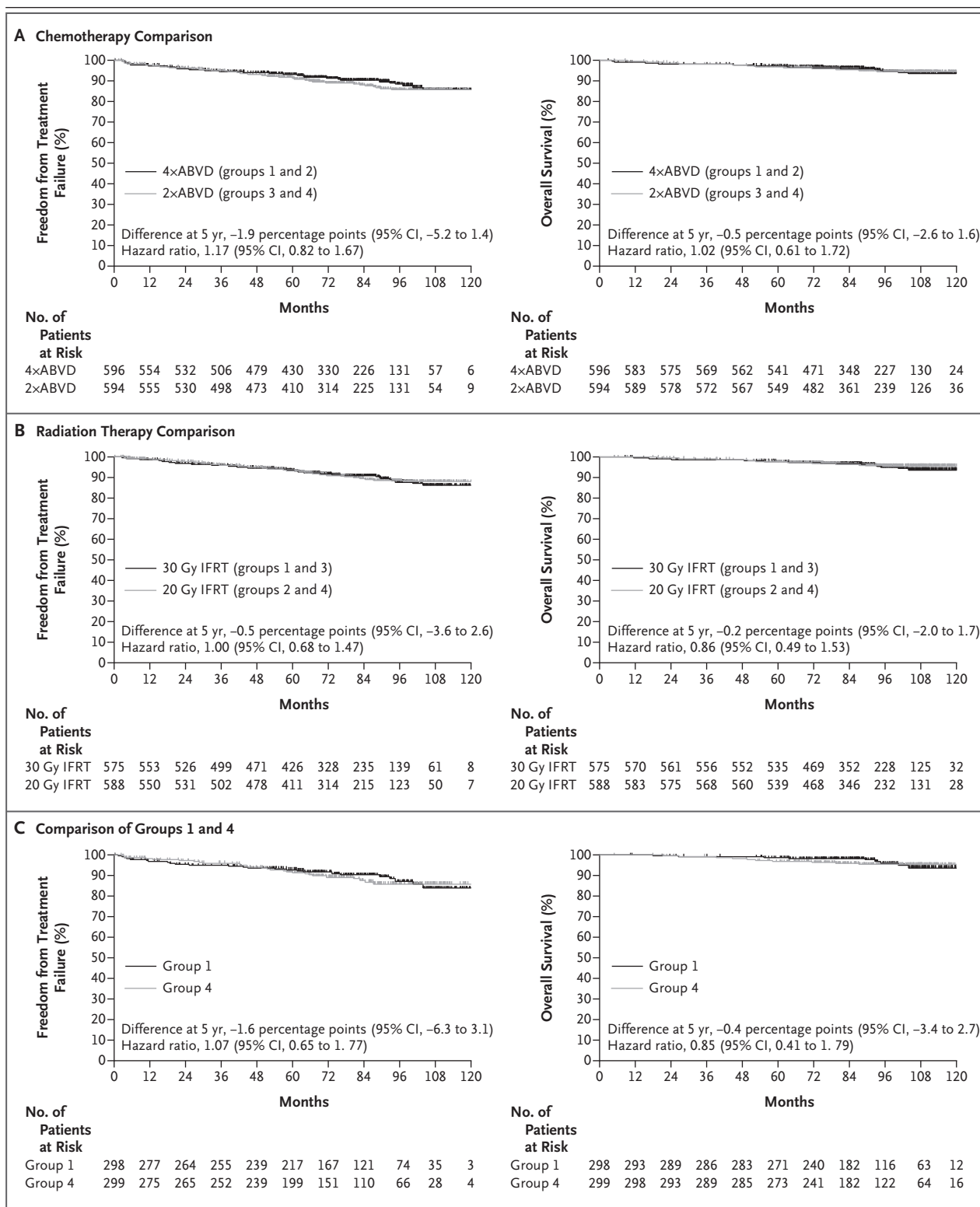
Figure 2 (facing page). Freedom from Treatment Failure and Overall Survival.

Two pooled treatment groups were compared with respect to chemotherapy regimens (groups 1 and 2 vs. groups 3 and 4) (Panel A) and radiation therapy doses (groups 1 and 3 vs. groups 2 and 4) (Panel B). Groups 1 and 4 were also compared (Panel C). Group differences with respect to freedom from treatment failure and overall survival at 5 years were estimated on the basis of Kaplan–Meier analyses, and hazard ratios were calculated with the use of Cox regression analysis (i.e., the comparison of the chemotherapy groups was stratified according to radiation therapy group, and vice versa). (For definitions of study end points, see the Supplementary Appendix, available with the full text of this article at NEJM.org.) Data for all patients were analyzed on the basis of the randomly assigned treatment groups (intention-to-treat principle). Data for overall survival were censored on the date when the information was last obtained; when the information lag exceeded 2 years, data on survival were obtained from registries, whenever possible. The median observation period for freedom from treatment failure was 79 months and that for overall survival was 91 months. The main analysis for the chemotherapy comparison included 1190 eligible patients who received at least 1 dose of the assigned study treatment. According to the protocol, 27 patients whose disease progressed or whose chemotherapy was discontinued before the start of radiation therapy were excluded from the main analysis for the radiation therapy comparison. (For methods and results of the sensitivity analyses, see the Supplementary Appendix.)

(95% CI, -5.2 to 1.4). The sensitivity analysis, based on treatment received per protocol, showed a 5-year estimated group difference of -2.3 percentage points (95% CI, -5.6 to 2.9). On the basis of these results, the predefined 7% inferiority of two cycles of ABVD plus radiation therapy can be excluded for the primary end point, freedom from treatment failure. The intention-to-treat analysis showed no significant differences between the two chemotherapy groups for the secondary end points of overall survival ($P=0.93$; hazard ratio for death, 1.02 [95% CI, 0.61 to 1.72]) and progression-free survival ($P=0.28$; hazard ratio for progression, relapse, or death from any cause, 1.22 [95% CI, 0.85 to 1.77]).

RADIATION THERAPY COMPARISON

In the intention-to-treat analysis of radiation therapy, the median observation time for the primary end point, freedom from treatment failure, was similar in the two groups: 77 months with 20 Gy and 80 months with 30 Gy. The rate of freedom from treatment failure at 5 years was 93.4% (95%



CI, 91.0 to 95.2) in the 30-Gy group and 92.9% (95% CI, 90.4 to 94.8) in the 20-Gy group (Table 3). The hazard ratio for treatment failure with 20 Gy as compared with 30 Gy was 1.00 (95% CI, 0.68 to 1.47). The 5-year estimated group difference (20 Gy vs. 30 Gy) was -0.5 percentage points (95% CI,

–3.6 to 2.6). The sensitivity analysis based on therapy received showed a 5-year estimated group difference of –0.2 percentage points (95% CI, –3.3 to 2.8). Thus, the predefined 7% inferiority of chemotherapy plus 20 Gy of radiation therapy can be excluded for the primary end point (freedom from treatment failure). The intention-to-treat analysis showed no significant differences between the radiation therapy groups for the secondary end points of overall survival ($P=0.61$; hazard ratio for death, 0.86 [95% CI, 0.49 to 1.53]) and progression-free survival ($P=0.98$; hazard ratio for progression, relapse, or death from any cause, 1.01 [95% CI, 0.68 to 1.48]). Overall, the rates of freedom from treatment failure might appear to be higher than those in a pure intention-to-treat analysis, since patients who dropped out before radiation therapy were excluded from this analysis. However, this was unlikely to affect between-group comparisons.

PRESPECIFIED REGRESSION ANALYSES

Prespecified factors included in the multivariate model were age above 50 years ($P<0.001$) and infradiaphragmatic disease ($P=0.24$), whereas male sex ($P=0.32$), systemic symptoms ($P=0.75$), and a low albumin level ($P=0.54$) were excluded. In the multivariate model including age, infradiaphragmatic involvement, and randomization group, no significant interaction was detected between the effects of the number of chemotherapy cycles and the radiation therapy dose.

COMPARISON OF GROUPS 1 AND 4

As shown in Figure 2, no significant difference in the rate of freedom from treatment failure was seen between groups 1 and 4 according to the stratified log-rank test ($P=0.79$). The 5-year estimate for the group difference was –1.6 percentage points (95% CI, –6.3 to 3.1), which is better than the noninferiority margin of –7 percentage points.

DISCUSSION

The aim of the HD10 study was to determine whether fewer cycles of chemotherapy and lower doses of radiation therapy could be delivered while maintaining high rates of disease control in patients with early Hodgkin's lymphoma and a favorable prognosis who were undergoing combined-approach treatment programs. No difference in efficacy was noted between the two-cycle

ABVD regimen and the four-cycle regimen when each was combined with involved-field radiation therapy. This was true for the primary end point, freedom from treatment failure at 5 years, as well as for all other efficacy end points, such as response, overall survival, and progression-free survival. The results were robust with longer follow-up (8 years). No differences were seen between the intention-to-treat and the per-protocol analyses. With regard to radiation therapy, the rate of freedom from treatment failure at 5 years was 93.4% (95% CI, 91.0 to 95.2) with 30 Gy of involved-field radiation therapy and 92.9% (95% CI, 90.4 to 94.8) with 20 Gy.

The results presented here show noninferiority for both fewer cycles of chemotherapy and a lower dose of radiation, on the basis of a noninferiority margin of 7 percentage points. However, confidence intervals were rather wide for differences in freedom from treatment failure and hazard ratios. Although the 5-year estimate for the group difference between the most intensive treatment and the least intensive treatment in this study was only 1.6 percentage points, a potential difference of 6.3 percentage points in favor of the more intensive treatment cannot be excluded and must be weighed against the reductions in acute and late toxicity, lower costs of treatment, and better quality of life associated with shorter and less intense treatment.

One of the key objectives in the treatment of Hodgkin's lymphoma is to reduce the intensity of first-line therapy as much as possible while maintaining tumor control. This is most relevant for early disease with a favorable prognosis, which accounts for about 30% of all cases of Hodgkin's lymphoma,¹ since overall survival rates are compromised by late treatment-related mortality.^{4–8} In the HD10 study, two cycles of ABVD as well as 20 Gy of radiation resulted in reduced rates of acute toxicity. Overall, 51.7% of patients treated with four cycles of ABVD had grade III or IV toxicity, as compared with 33.2% of those receiving two cycles ($P<0.001$). The rates of acute toxicity (grade III or IV) were also higher among patients treated with 30 Gy of involved-field radiation therapy than among those receiving 20 Gy (8.7% vs. 2.9%, $P<0.001$). Although there were numerical differences between the radiation therapy groups with respect to secondary cancers (24 [4.1%] vs. 31 [5.4%]), these findings were not significant and might have been due to chance. Clearly, longer

follow-up is needed to identify differences in long-term toxicity, such as secondary neoplasia and severe organ damage, among different treatment approaches. Given that many of the late, fatal complications of radiation therapy do not emerge until the second decade after treatment, our data cannot speak to the effect of treatment on overall survival.

Since radiation therapy is associated with the development of secondary solid tumors 5 to 25 years after initial treatment,⁴⁻⁸ some groups advocate the use of chemotherapy alone for patients with early-stage Hodgkin's lymphoma. Usually, six cycles of ABVD are given, and there has been some controversy on this issue.¹⁵⁻¹⁹ For this group of patients, combined-approach treatment programs have provided superior tumor control when compared directly with chemotherapy alone in some studies²⁰⁻²⁴ but not in others.^{15,19} Currently, combined-approach treatment programs are widely used as the treatment of choice in early-stage Hodgkin's lymphoma, and our study suggests that a shorter chemotherapy regimen with a lower radiation dose preserves a high level of disease control. With an overall survival rate of 95.1% at 8 years, some patients may still be overtreated.

However, the established clinical risk factors, which are based on measures such as the International Prognostic Score,²⁵ currently do not allow identification of patients who can be cured with even less treatment. The use of positron-emission

tomography (PET) might help to discriminate between patients at low risk and those at high risk, both early in the course of chemotherapy²⁶ and after its completion.²⁷ The potential effect of PET in patients with Hodgkin's lymphoma has also been suggested in a number of retrospective, non-randomized studies.²⁸⁻³⁰ Several ongoing trials are evaluating the role of PET in identifying patients with early Hodgkin's lymphoma and a favorable prognosis who might not need additional radiation therapy after two cycles of ABVD (the German Hodgkin Study Group Hodgkin Disease 16 [the current GHSG HD16] trial [ClinicalTrials.gov number, NCT00736320]) or after three cycles of ABVD (the European Organization for Research and Treatment of Cancer [EORTC H10F] trial [ClinicalTrials.gov number, NCT00433433] and others).

In summary, the HD10 trial showed that in patients with early-stage Hodgkin's lymphoma and a favorable prognosis, treatment with two cycles of ABVD followed by 20 Gy of involved-field radiation therapy is as effective as, and less toxic than, four cycles of ABVD followed by 30 Gy of involved-field radiation therapy.

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APPENDIX

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Dose-Intensification in Early Unfavorable Hodgkin's Lymphoma: Final Analysis of the German Hodgkin Study Group HD14 Trial

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Processed as a Rapid Communication manuscript. See accompanying editorial on page 895; listen to the podcast by Dr Armitage at www.jco.org/podcasts

ABSTRACT

Purpose

In patients with early unfavorable Hodgkin's lymphoma (HL), combined modality treatment with four cycles of ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) and 30 Gy involved-field radiotherapy (IFRT) results in long-term tumor control of approximately 80%. We aimed to improve these results using more intensive chemotherapy.

Patients and Methods

Patients with newly diagnosed early unfavorable HL were randomly assigned to either four cycles of ABVD or an intensified treatment consisting of two cycles of escalated BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone) followed by two cycles of ABVD (2 + 2). Chemotherapy was followed by 30 Gy IFRT in both arms. The primary end point was freedom from treatment failure (FFTF); secondary end points included progression-free survival (PFS) and treatment-related toxicity.

Results

With a total of 1,528 qualified patients included, the 2 + 2 regimen demonstrated superior FFTF compared with four cycles of ABVD ($P < .001$; hazard ratio, 0.44; 95% CI, 0.30 to 0.66), with a difference of 7.2% at 5 years (95% CI, 3.8 to 10.5). The difference in 5-year PFS was 6.2% (95% CI, 3.0% to 9.5%). There was more acute toxicity associated with 2 + 2 than with ABVD, but there were no overall differences in treatment-related mortality or secondary malignancies.

Conclusion

Intensified chemotherapy with two cycles of BEACOPP escalated followed by two cycles of ABVD followed by IFRT significantly improves tumor control in patients with early unfavorable HL.

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INTRODUCTION

To date, the standard treatment of early unfavorable Hodgkin's lymphoma (HL) for most cooperative groups is combined modality treatment with four cycles of ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) and 30 Gy involved-field radiotherapy (IFRT).¹⁻³ This results in approximately 80% long-term tumor control, which is not satisfying when compared with results in early favorable HL.⁴ Earlier attempts using BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone) in baseline dose did not improve results, as demonstrated in the GHSG (German Hodgkin Study Group) HD11 study.⁵ On the basis of the high efficacy of

BEACOPP escalated (BEACOPPesc) in advanced stages,^{6,7} we decided to evaluate this dose-intensified regimen in early unfavorable HL. The randomized GHSG HD14 trial thus compared four cycles of ABVD (standard arm) with two cycles BEACOPPesc followed by two cycles of ABVD (2 + 2). Here we report the final results of this trial.

PATIENTS AND METHODS

The HD14 protocol was designed by the GHSG steering committee and approved by the ethics committees of participating centers (Data Supplement). An independent data safety committee monitored patient safety and efficacy of treatment throughout the study period. When the third planned interim analysis yielded a significant group

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sequential test (adjusted overall $P = .0452$), the trial was stopped according to protocol. Randomization was discontinued on July 10, 2008, and the final analysis was scheduled so that all randomly assigned patients would have been followed for at least 1 year after final restaging.

Patients

Entry into the trial was restricted to patients with stage IA, IB, or IIA histologically proven HL with at least one of the following risk factors: bulky mediastinal mass ($\geq$ one third maximum transverse thorax diameter); extranodal involvement; erythrocyte sedimentation rate (ESR) ≥ 50 mm/h (without B symptoms) or ESR ≥ 30 mm/h (with B symptoms); or three or more lymph node areas involved. Patients with stage IIB disease with either of the latter two risk factors were also included.

After initial diagnosis by the local pathologist, biopsy material was centrally reviewed by at least one member of a panel of six HL pathology experts. All patients provided written informed consent before study entry according to the Good Clinical Practice guidelines of the International Conference on Harmonisation and national regulations.

Study Design

Patients were recruited and treated in 407 hospitals and practices in Germany, Switzerland, the Netherlands, the Czech Republic, and Austria. After written informed consent and clinical staging, patients were registered at the GHSG central trial office by telephone and then randomly assigned at an allocation ratio of 1:1 to standard arm A with four cycles of ABVD or to the experimental arm B with 2 + 2 chemotherapy. Standard 30 Gy IFRT was administered as consolidation therapy in both arms. Stratification factors for randomization included participating center, age, constitutional symptoms, large mediastinal tumor or bulky disease, and supra- or infradiaphragmatic involvement.

Study Conduct

ABVD was administered at standard doses consisting of doxorubicin 25 mg/m² (days 1 and 15), bleomycin 10 mg/m² (days 1 and 15), vinblastine 6 mg/m² (days 1 and 15), and dacarbazine 375 mg/m² (days 1 and 15), repeated on day 29. Granulocyte colony-stimulating factor was administered if clinically indicated, starting from day 7 or 21. BEACOPPesc included cyclophosphamide 1,250 mg/m² (day 1), doxorubicin 35 mg/m² (day 1), etoposide 200 mg/m² (days 1 to 3), procarbazine 100 mg/m² (days 1 to 7), prednisone 40 mg/m² (days 1 to 14), vincristine 1.4 mg/m² (day 8; maximum, 2 mg), and bleomycin 10 mg/m² (day 8), repeated on day 22. Granulocyte colony-stimulating factor had to be administered from day 8 of each BEACOPPesc cycle until recovery of WBC to at least 1,000/ μ L on 3 consecutive days. Treatment was postponed until recovery of WBC to at least 2,500/ μ L and platelet count to at least 80,000/ μ L on the day scheduled for re-treatment. In cases of treatment postponement of more than 2 weeks or pronounced toxicity during treatment, dose reductions were foreseen in the trial protocol.

RT

On the basis of the initial staging, the expert RT panel provided an individual RT plan for each patient. All patients received 30 Gy IFRT in single fractions of 1.8 to 2.0 Gy administered five times per week.

End Points

The primary efficacy end point was freedom from treatment failure (FFTF); secondary end points included overall survival (OS), progression-free survival (PFS), response rates, and treatment-related toxicity.

Statistical Methods

This trial employed a two-arm parallel group design aimed at demonstrating superiority of the 2 + 2 regimen compared with four cycles of ABVD with respect to the primary end point of FFTF. To detect the need for early termination, a group sequential design with five interim analyses was planned.

Assessment of Treatment Effects

The trial was analyzed using group sequential methods⁸⁻¹⁰ with appropriately adjusted CIs and P values for the primary end point of FFTF. Time-to-event end points were compared between groups using the Kaplan-Meier method and log-rank tests for P values as well as univariate Cox regression for hazard ratios (HRs). To detect a possible impact of prognostic factors, pre-

planned multivariate Cox regressions were performed as sensitivity analyses on the same analysis sets. Outcomes and toxicity rates were analyzed using Fisher's exact test. Design and analysis of the trial were carried out using SAS versions 8 to 9.2 (SAS Institute, Cary, NC) and ADDPLAN versions 3.1 to 5 (ADDPLAN, Cologne, Germany).

Analysis Sets

The full analysis set (FAS) consisted of all randomly assigned patients with confirmed histology. According to the trial protocol, patients with violations of major inclusion or exclusion criteria as well as withdrawals before start of therapy had to be excluded from the primary analysis set of qualified patients (QAS). Sensitivity analyses of efficacy end points were carried out on the FAS as well as on the per-protocol analysis set (PAS). Criteria to exclude patients from the PAS apart from violation of major inclusion or exclusion criteria were change of treatment arm, early treatment discontinuation, or relevant dose deviations of chemotherapy, unless resulting from death or progression.

RESULTS

Patients

Between January 2003 and July 2008, 1,655 patients with histologically confirmed early unfavorable HL were recruited (Fig 1). Because of insufficient documentation, 32 patients were excluded from all analyses. Therefore, the FAS comprised 1,623 patients; 818 were randomly assigned to arm A and 805 to arm B. Seven patients who withdrew from the trial before starting chemotherapy and 88 patients with major inclusion or exclusion criteria violations were excluded from the QAS, which was the main analysis set for the arm comparison and comprised 1,528 patients (765 in arm A; 763 in arm B). Because they did not receive the assigned treatment, or because adherence to protocol could not be confirmed, 97 QAS patients were excluded from the PAS.

Demographic baseline characteristics, stage of disease, and risk factors of patients were well balanced between treatment arms (Appendix Table A1, online only). In the QAS, 53.3% of patients were women. The median age was 32 years (range, 18 to 60 years); 9.4% were older than 50 years of age; 4.8% of patients had stage I disease (2.6% IA; 2.2% IB); 95.2% had stage II disease (67.5% IIA; 27.7% IIB). The most common risk factor was three or more involved lymph node areas (69.7%), followed by high ESR (52.9%), large mediastinal mass (18.7%), and extranodal involvement (8.1%). Localized infradiaphragmatic disease was present in 5.6% of patients.

A histologic review was performed in 86.4% of patients. The most frequent histologic subtypes were nodular sclerosis (70.3%) and mixed cellularity (18.2%).

Dose Delivery

As defined in the study protocol (Appendix Table A2, online only), 97.8% of evaluable QAS patients received four cycles of chemotherapy. In both arms, chemotherapy was administered according to protocol in most cases, with no difference between arms (relative total doses [$\pm$ standard deviation] were 98.8 ± 4.7 and 97.6 ± 4.2 in arms A and B, respectively). Dose-intensity was also identical (0.9 ± 0.1).

Safety and Adverse Event Profiles

During chemotherapy, acute toxicity (WHO grade 3 to 4; Table 1) was significantly more frequent in arm B (87.1%) as compared with arm A (50.7%), with at least one grade 4 toxicity in 56.6% (arm B) and

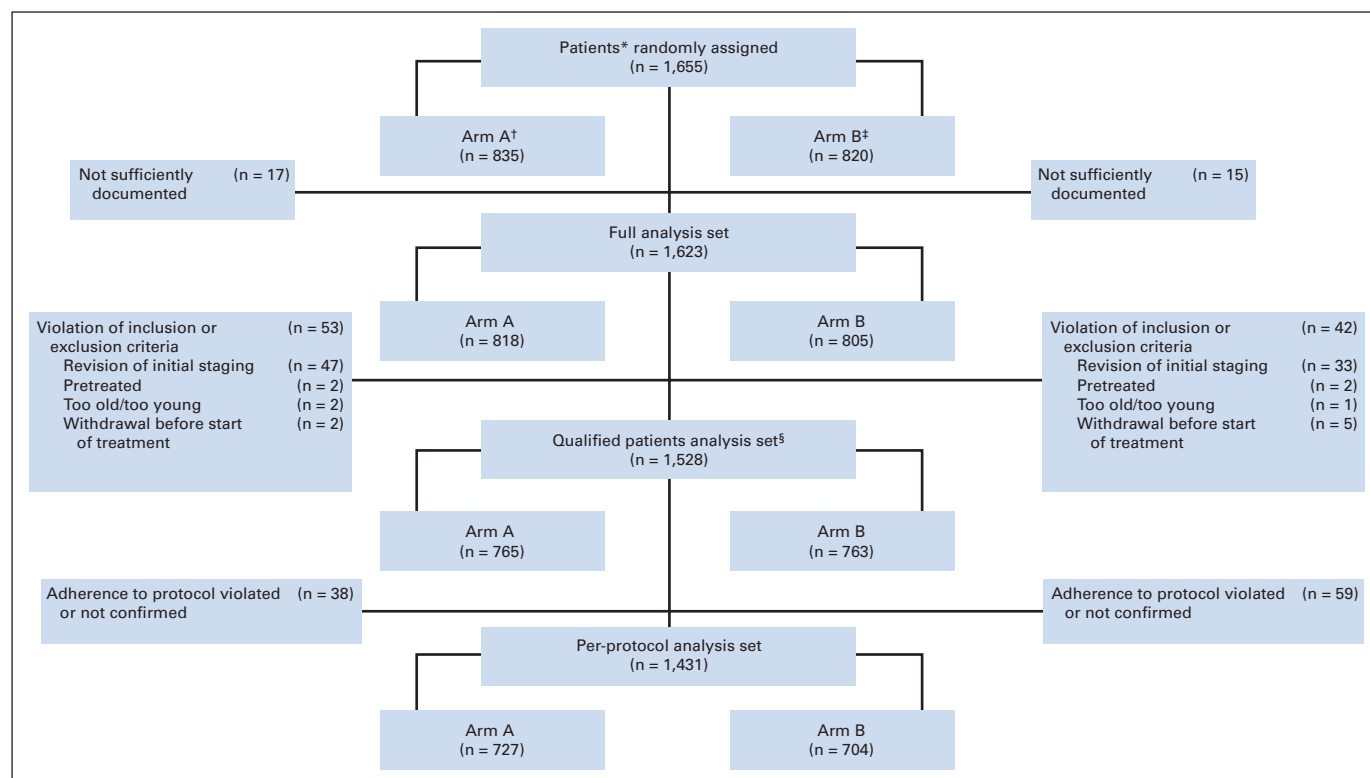


Fig 1. CONSORT diagram. (*) Patients were assessed for eligibility at individual trial centers, and histology was confirmed before registration and random assignment at the central trial office. (†) Arm A received four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) plus 30 Gy involved-field radiotherapy (IFRT). (‡) Arm B received two cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, plus two cycles of ABVD plus 30 Gy IFRT. (§) The qualified patient analysis set is the primary analysis set according to the trial protocol.

5.9% (arm A), respectively. Four patients (0.52%) died as a result of acute toxicity in first-line therapy; all were treated in arm B. Most frequent toxicities were myelosuppression and hair loss in both arms. As expected, there was more acute toxicity associated with BEACOPPesc than with ABVD. Interestingly, there was also more toxicity associated with ABVD when administered after two cycles of BEACOPPesc than after two cycles of ABVD. The inclusion of non-qualified patients in a sensitivity analysis did not lead to additional findings on safety or feasibility (data not shown).

After a median follow-up of 43 months, 36 (2.4%) of 1,528 QAS patients had died (Table 2). The main reasons were secondary malignancies ($n = 8$), HL ($n = 7$), and toxicity of salvage therapy ($n = 7$). Overall, 32 secondary malignancies occurred in the QAS (arm A, 17 instances [2.2%]; arm B, 15 instances [2.0%]). Because of the low number of events, there were no statistically relevant differences in the total number of deaths or secondary neoplasms between treatment arms.

Efficacy

The overall complete response/unconfirmed complete response rate in the QAS was 95.4% (Appendix Table A3, online only), with no arm difference ($P = .6272$). With a median observation time of 43 months, the reported progression/relapse rate was 5.4% overall (Table 2), with 2.5% in arm B and 8.4% in arm A. More patients in arm A than in arm B had a second relapse (1.4% ν 0.4%), but there were not enough events to yield a significant arm difference.

As shown in Figures 2A to 2C (and Appendix Table A4, online only), OS was 97.0% at 5 years (95% CI, 95.9% to 98.1%) and did not

differ between treatment arms ($P = .7308$). For the primary end point of FTF, superiority of arm B was established by a significant group sequential test in the third planned interim analysis, with an adjusted two-sided overall P value of .0451. In the final analysis, the nonadjusted P value was $< .001$ (HR, 0.44; 95% CI, 0.30 to 0.66). Five-year FTF rates of 87.7% (95% CI, 84.8% to 90.6%) and 94.8% (95% CI, 93.1% to 96.6%) in arms A and B, respectively, resulted in a difference of 7.2% (95% CI, 3.8% to 10.5%). PFS was also significantly better in arm B on the adjusted 2.5% level (HR, 0.45; 95% CI, 0.30 to 0.69; $P < .001$). The difference in 5-year PFS rates was 6.2% (95% CI, 3.0% to 9.5%). Thus, superiority of arm B in terms of FTF as well as PFS can be concluded. Prespecified sensitivity analyses performed on the FAS and PAS yielded similar results (Appendix Figs A1A to A1D, online only).

Of the 64 patients experiencing relapse or progression after four cycles of ABVD, 12 (19%) died. Median survival time after diagnosis of first progression or relapse was 15 months (range, 3.6 to 42.7 months). Sixteen survivors were lost to follow-up within 1 year after diagnosis of HL progression or relapse. Thirty-six patients underwent successful salvage therapy and had a median observation time after first progression or relapse of 34 months (range, 12.9 to 73.4 months). In the 2 + 2 arm, six (32%) of 19 patients died after first-line therapy failure. Their median survival time after diagnosis of first progression or relapse was 12 months (range, 1.2 to 22.4 months). Four survivors were lost to follow-up within 1 year after diagnosis of HL progression or relapse. Nine patients underwent successful salvage therapy and had a median observation time after first progression or relapse of 38 months (range, 15.0 to 60.6 months).

Table 1. Acute Toxicities of Chemotherapy

Toxicity‡	Treatment Arm*†			
	A (n = 757)		B (n = 744)	
	No. of Patients	%	No. of Patients	%
At least one toxicity during treatment§	384 of 757	50.7	648 of 744	87.1
Chemotherapy cycle				
1	175 of 761	23.0	501 of 745	67.2
2	226 of 760	29.7	549 of 742	74.0
3	263 of 756	34.8	429 of 729	58.8
4	254 of 748	34.0	402 of 723	55.6
At least one hematologic toxicity during treatment§	182 of 757	24.0	597 of 744	80.2
Chemotherapy cycle				
1	92 of 761	12.1	433 of 745	58.1
2	86 of 760	11.3	468 of 742	63.1
3	84 of 756	11.1	273 of 729	37.4
4	80 of 748	10.7	244 of 723	33.7
Type of acute toxicity				
Anemia	7	0.9	67	9.0
Thrombopenia	1	0.1	163	21.9
Leukopenia	178	23.5	588	79.0
Nausea/vomiting	104	13.7	76	10.2
Mucositis	3	0.4	32	4.3
GI tract	14	1.8	43	5.8
Urogenital tract	2	0.3	0	0
Respiratory tract	11	1.5	13	1.7
Drug fever	6	0.8	17	2.3
Allergy	2	0.3	12	1.6
Heart	2	0.3	1	0.1
Hair	179	23.6	356	47.8
Infection	26	3.4	54	7.3
Skin	8	1.1	2	0.3
Pain	27	3.6	54	7.3
Nervous system	6	0.8	24	3.2

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; IFRT, involved-field radiotherapy.

*Of 1,528 qualified patients, 1,506 (arm A, 761; arm B, 745) were documented for acute toxicities for at least one cycle, and 1,501 (arm A, 757; arm B, 744) were documented for acute toxicities for all cycles administered. Patients were analyzed according to arm as treated.

†Arm A received four cycles of ABVD plus 30 Gy IFRT; arm B received two cycles of BEACOPP plus two cycles of ABVD plus 30 Gy IFRT.

‡Toxicity of WHO grade III or IV only.

§ $P < .001$.

Prognostic Factors and Subgroup Analyses

The only significant ($P < .05$) predictors for PFS events in the univariate regression analysis were large mediastinal mass and elevated ESR. Other factors such as extranodal disease, more than two involved regions, infradiaphragmatic disease, B symptoms, sex, and age were not significant. In a multivariate model for PFS including all these factors as well as treatment arm, the same two risk factors and treatment arm were significant, with estimated HRs of 2.4 (large mediastinal mass), 2.1 (elevated ESR), and 2.3 (arm A). In posthoc subgroup analyses of the FAS, patients with at least one of the two significant risk factors (high-risk group [$n = 1,013$]; 81 failure events for PFS) were compared with patients without any of these risk factors (low-risk group [$n = 610$]; 25 failure events). Five-year PFS was 94.0% (95% CI, 91.3% to 96.7%) in the low-risk group, compared with 91.2% (95% CI, 89.3% to 93.2%) in the high-risk group. The inferiority of the high-risk group was more pronounced for patients in arm A ($P = .0072$) than in arm B ($P = .1071$), but it should be noted that there was not enough power to detect an interaction between treatment arm and risk group (Appendix Figs A2A to A2D, online only). A

subgroup analysis with large mediastinal mass and stage IIB as risk factors demonstrated similar results (Appendix Figs A3A, A3B, online only).

DISCUSSION

The GHSG HD14 trial compared intensified chemotherapy consisting of two cycles of BEACOPPesc followed by two cycles of ABVD (2 + 2) with the previous standard of four cycles of ABVD to improve tumor control in patients with early unfavorable HL. All patients received 30 Gy IFRT after chemotherapy. The intensified 2 + 2 arm was clearly superior in terms of FFTF and PFS, despite moderately higher acute toxicity.

In contrast to significant improvements in early favorable and advanced stage HL,^{4,6} no significant progress has recently been reported for early unfavorable HL. More aggressive regimens such as BEACOPP baseline were evaluated, but neither the EORTC (European Organisation for Research and Treatment of Cancer) H9-U

Table 2. Failure Events and Late Effects*

Event/Effect	Treatment Arm†			
	A (n = 765)		B (n = 763)	
	No. of Patients	%	No. of Patients	%
Death resulting from:‡	17	2.2	19	2.5
HL	3		4	
Toxicity of study chemotherapy	0		4	
Toxicity of salvage therapy	6		1	
Secondary neoplasia	5		3	
Suicide	1		0	
Respiratory	0		2	
Brain	0		1	
Other disease	1		3	
Unclear	1		1	
Progression or first relapse§	64	8.4	19	2.5
Progression	23	3.0	6	0.8
Early relapse	23	3.0	7	0.9
Late relapse	18	2.4	6	0.8
Second relapse	11		3	
Secondary malignancy¶	17	2.2	15	2.0
AML/MDS	0		2	
NHL	9		5	
Solid tumor	8		8	

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AML, acute myeloid leukemia; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; FAS, full analysis set; HL, Hodgkin's lymphoma; IFRT, involved-field radiotherapy; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma.

*Median observation time, 43 months (95% CI, 41.5 to 43.6).

†Total of 1,528 qualified patients were analyzed according to arm as randomly assigned. Arm A received four cycles of ABVD plus 30 Gy IFRT; arm B received two cycles of BEACOPP plus two cycles of ABVD plus 30 Gy IFRT.

‡Four additional patients in the FAS who were not qualified died as a result of second malignancy (n = 2) and HL (n = 2).

§P < .001.

||P = .0563.

¶Three nonqualified patients in the FAS also had a secondary neoplasm.

study¹¹ nor the GHSG HD11 trial⁵ demonstrated better tumor control over ABVD. According to a mathematic effective dose (ED) model¹² assessing the relative potency of individual drugs in patients with HL, the ED of the newly developed 2 + 2 regimen was higher when compared with that of four cycles of ABVD (17.3 v 15.0) and four cycles of BEACOPP baseline (17.3 v 15.2).¹³ In line with these calculations, HD14 demonstrates significantly better tumor control with 2 + 2 than with four cycles of ABVD in early unfavorable HL.

The improved efficacy of the 2 + 2 regimen comes at the price of more acute toxicity. There was significantly more severe (WHO grades 3 to 4) hematologic toxicity with 2 + 2 (87.1%) as compared with four cycles of ABVD (50.7%); acute treatment-related mortality in the 2 + 2 arm was 0.52%. The more pronounced acute toxicity of 2 + 2 is counterbalanced by fewer relapses and fewer patients with progressive disease. Taken together, these result in a 6.2% PFS advantage for 2 + 2 at 5 years. Because more than 50% of relapsed or progressing patients in both arms underwent successful salvage therapy, OS was not significantly different, despite the higher rate of relapse/progression in arm A.

The clinical impact of this new regimen might be challenged by putatively increased long-term toxicity of 2 + 2. However, a more detailed analysis of the current data contradicts this view. First, the

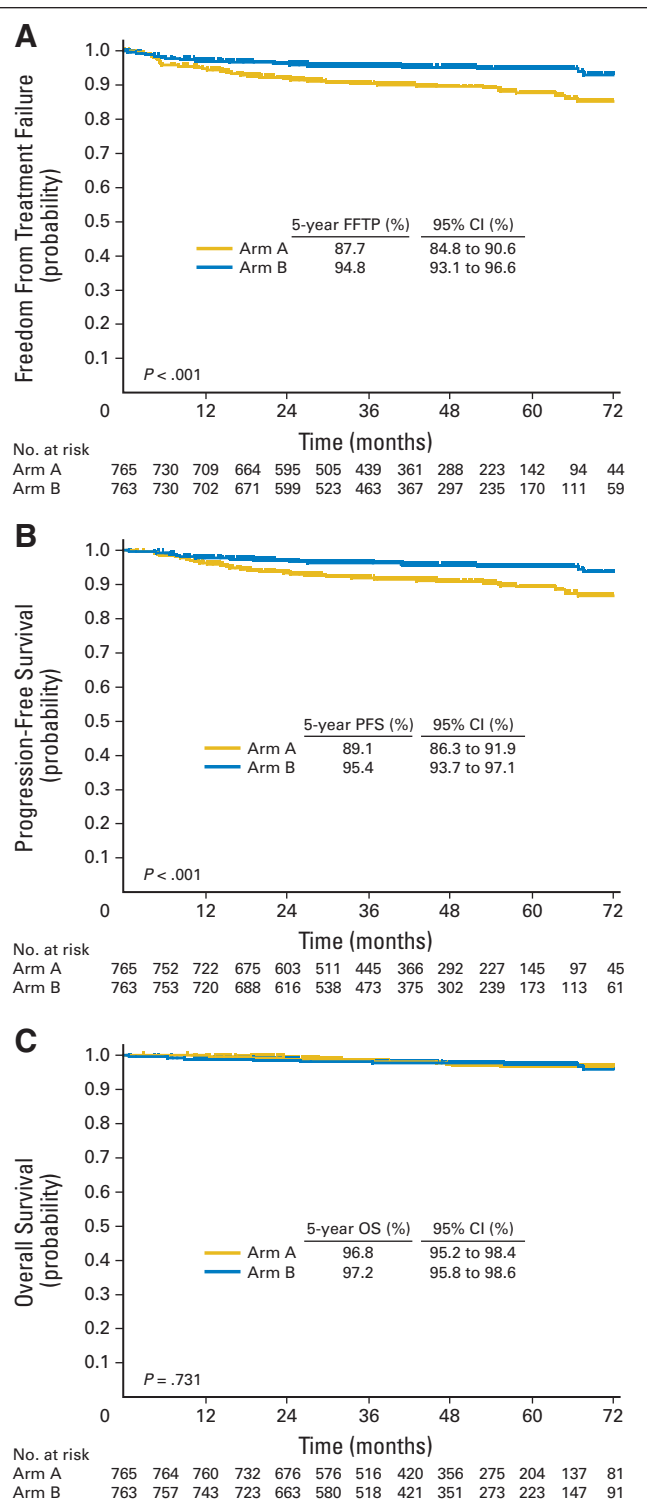


Fig 2. Kaplan-Meier curves for the primary (ie, qualified patients) analysis set of the HD14 study. (A) Freedom from treatment failure (FFTF); (B) progression-free survival (PFS); (C) overall survival (OS). Arm A received four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) plus 30 Gy involved-field radiotherapy (IFRT); arm B received two cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, plus two cycles of ABVD plus 30 Gy IFRT. Median observation time was 43 months.

lower number of patients experiencing progression or relapse in the 2 + 2 arm (2.5% v 8.4%; $P < .001$) saved a significant number of patients from additional treatment including high-dose chemotherapy and the related acute and long-term toxicities.¹⁴ Second, the higher rate of patients experiencing progression or relapse after four cycles of ABVD also resulted in a higher proportion of patients (1.4% v 0.4%) experiencing second relapses, for whom treatment is often palliative. Third, although a higher rate of long-term toxicity after 2 + 2 can be discussed, the total number of secondary malignancies in HD14 was similar in both arms. In addition, a recent GHSG analysis revealed no significant differences in female fertility after four cycles of ABVD or 2 + 2.^{14a} Taken together, these data provide the rationale for choosing 2 + 2 as new GHSG standard for early unfavorable HL.

Large mediastinal mass and elevated ESR were adverse prognostic factors in multivariate models for FFTR and PFS in the present trial. In posthoc subgroup analyses, patients with at least one of these risk factors had pronounced PFS inferiority in arm A in comparison with those in arm B. Although the analyses were not powered to detect an interaction between treatment arm and risk group, they suggest that patients with mediastinal mass or elevated ESR particularly benefit from the intensified chemotherapy. In future trials, these risk factors might be used for more personalized treatment approaches in early unfavorable HL, together with other approaches such as positron emission tomography (PET)¹⁵ or new biomarkers.¹⁶

The preceding GHSG HD11 study revealed that modestly intensified chemotherapy with BEACOPP baseline and consolidating IFRT with a reduced RT dose of 20 Gy resulted in outcomes similar to those of four cycles of ABVD followed by 30 Gy IFRT.⁵ Given the higher ED of 2 + 2, it is reasonable to assume that patients might be spared the additional toxicity¹⁷ of 30 Gy IFRT after 2 + 2 chemotherapy. Therefore, the next GHSG trial for early unfavorable HL (HD17) will compare a risk-stratified RT reduction as the experimental arm versus 2 + 2 plus 30 Gy IFRT as the standard arm. Because PET after chemotherapy has been shown to discriminate low- from high-risk HL,¹⁸ patients in the experimental arm of HD17 with negative PET after chemotherapy will not receive RT, whereas patients with positive PET will be treated with a reduced radiation field volume applying 30 Gy involved node RT (INRT).^{19,20} PET-based reduction of RT in early stage HL has already been evaluated in the EORTC/GELA (Groupe d'Etude des Lymphomes de l'Adulte)/ILL (Intergruppo Italiano Linfomi) H10 trial. Early unfavorable patients in the standard arm received four cycles of ABVD followed by 30 Gy INRT, whereas patients in the experimental arm were treated with two cycles of ABVD fol-

lowed by four cycles of ABVD for patients with negative PET and two cycles of BEACOPPesc and 30 Gy INRT for patients with positive PET. However, this trial was closed early because of more events in the arms without additional RT.²¹ On the basis of the superior PFS of the new 2 + 2 regimen over four cycles of ABVD, we hypothesize that 2 + 2 will be a more resilient backbone for the PET-guided omission of RT in early unfavorable HL in the HD17 trial.

In conclusion, a dose-intensification with two cycles of BEACOPPesc followed by two cycles of ABVD results in better tumor control with increased PFS as compared with standard treatment with four cycles of ABVD. The increased rate of acute toxicities in the intensified arm is overcome by fewer relapses and less second-line toxicity. The regimen of 2 + 2 plus 30 Gy IFRT is the new GHSG standard for patients with early unfavorable HL age 60 years or younger.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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3. Intenzifikace léčby pokročilých stadií Hodgkinova lymfomu

Léčba pokročilých stadií HL, definovaných podle klasifikace Ann Arbor jako klinické stadium III a IV, případně stadium IIB s přítomností nepříznivých rizikových faktorů, prošla během posledních desetiletí také významným vývojem. Zatímco u časných stadií onemocnění bylo hlavním cílem postupné snižování intenzity léčby při zachování vysoké účinnosti, u pokročilých stadií se léčebné strategie dlouhodobě zaměřovaly především na zvýšení pravděpodobnosti trvalého vyléčení za cenu intenzivnější systémové léčby. V posledních letech se však pozornost přesouvá také k individualizaci léčby podle časně léčebné odpovědi a k využití cílených léčiv a imunoterapie s cílem zachovat vysokou účinnost při současném snížení akutní i pozdní toxicity.⁴⁷

Významný průlom v léčbě pokročilého HL představovalo zavedení kombinované chemoterapie MOPP (mechlorethamin, vinkristin, prokarbazin a prednison), kterou na přelomu 60. a 70. let vyvinul Vincent T. DeVita se spolupracovníky.⁴ Režim MOPP jako první prokázal, že i pokročilé diseminované stadium HL lze u významné části pacientů dlouhodobě vyléčit systémovou chemoterapií. Přestože představoval zásadní změnu v léčbě tohoto onemocnění, jeho širší využití bylo limitováno vysokou akutní i pozdní toxicitou, zejména výraznou gonadotoxicitou a zvýšeným rizikem sekundárních myeloidních malignit. Snahou o zachování vysoké účinnosti při příznivějším bezpečnostním profilu vznikl v polovině 70. let režim ABVD (doxorubicin, bleomycin, vinblastin a dakarbazin), který se stal základem moderní léčby HL.⁵ Randomizovaná studie Canellose a spolupracovníků následně prokázala vyšší účinnost režimu ABVD ve srovnání s MOPP při současně nižším výskytu závažných pozdních nežádoucích účinků, zejména sekundárních hematologických malignit a poruch fertility.³⁸ Díky příznivému poměru mezi účinností a toxicitou se režim ABVD stal na více než tři desetiletí mezinárodním standardem léčby pokročilého HL.

Přestože režim ABVD umožnil dosáhnout dlouhodobé remise u většiny nemocných, u části pacientů přetrvávalo významné riziko časného relapsu nebo rozvoje refrakterního HL. To vedlo Německou studijní skupinu pro Hodgkinův lymfom (German Hodgkin Study Group, GHSG) k vývoji intenzifikovaného režimu eskalovaný BEACOPP (eBEACOPP), jehož cílem bylo zvýšit protinádorovou účinnost zejména u pacientů s pokročilým onemocněním.⁴⁸ Zásadní význam měla studie GHSG HD9, která prokázala, že léčba režimem eskalovaný BEACOPP vede ve srovnání se standardním

režimem COPP/ABVD k významnému zlepšení kontroly onemocnění i celkového přežití.^{48,49} Uvedená studie tak poprvé ukázala, že zvýšení dávkové intenzity může u vybraných pacientů zlepšit dlouhodobé léčebné výsledky. Vyšší účinnost však byla provázena podstatně vyšší hematologickou toxicitou, vyšším výskytem infekčních komplikací, sekundárních myeloidních malignit i gonadálního poškození.

Na závěry studie GHSG HD9 navázala studie GHSG HD15, která potvrdila možnost snížení intenzivní léčby pokročilého HL při zachování dlouhodobé účinnosti. Prokázala, že zkrácení léčby z osmi na šest cyklů eskalovaného BEACOPP zachovává dlouhodobou účinnost při současném snížení kumulativní toxicity léčby. Současně jako první velká randomizovaná studie systematicky využila PET/CT po ukončení chemoterapie k rozhodování o indikaci konsolidační radioterapie reziduálních ložisek. Desetileté výsledky studie potvrdily vysokou účinnost tohoto přístupu i jeho příznivý dlouhodobý bezpečnostní profil, čímž byl režim 6 cyklů eBEACOPP následovaný PET-řízenou radioterapií potvrzen jako standard léčby pokročilého HL v rámci GHSG.²¹

Další významný posun v léčbě pokročilého HL přineslo zavedení vyšetření PET/CT v průběhu léčby (interim PET/CT), které umožnilo přizpůsobit intenzitu léčby časné metabolické odpovědi nádoru. Studie RATHL prokázala, že u pacientů s negativním interim PET po dvou cyklech ABVD lze bezpečně vynechat bleomycin v dalších cyklech léčby, aniž by došlo ke zhoršení léčebných výsledků, při současném významném snížení rizika plicní toxicity.¹⁵ Ve studii AHL2011 bylo obdobně prokázáno, že u nemocných s negativním PET po úvodní intenzivní léčbě lze bezpečně deeskalovat terapii z režimu eBEACOPP na ABVD, což vedlo ke snížení toxicity při zachování vysoké účinnosti léčby.²² Tyto studie položily základy současné PET-adaptované léčby, která umožňuje individualizovat intenzitu terapie podle časné léčebné odpovědi.

Další vývoj léčebných strategií byl spojen se zařazením cílené léčby do první linie. Přelom představovala studie ECHELON-1, která prokázala lepší léčebné výsledky režimu A+AVD, v němž byl bleomycin nahrazen brentuximab vedotinem, ve srovnání se standardním režimem ABVD.²³ Dlouhodobé sledování následně potvrdilo nejen přetrvávající zlepšení přežití bez progresu, ale také statisticky významný přínos v celkovém přežití, čímž se režim A+AVD stal jednou z nových terapeutických možností první linie léčby pokročilého HL.⁵⁰

Na zkušenosti s intenzivní léčbou navázala studie GHSG HD21, která hodnotila nový režim BrECADD, obsahující brentuximab vedotin, jako alternativu k eskalovanému BEACOPP. Studie prokázala, že při zachování velmi vysoké účinnosti lze významně snížit akutní i pozdní toxicitu léčby, včetně gonadálního poškození, a představuje tak další krok k optimalizaci intenzivní léčby pokročilého HL.²⁴

Nejnovější vývoj léčby je spojen se začleněním inhibitorů kontrolních bodů imunitní odpovědi (ICI) do první linie léčby. Studie SWOG S1826 prokázala, že kombinace nivolumabu s režimem AVD dosahuje lepších výsledků než režim brentuximab vedotin+AVD při současně velmi příznivém bezpečnostním profilu.⁵¹ Výsledky této studie naznačují, že imunoterapie se může stát základem budoucí léčby pokročilého HL v první linii. Vývoj léčby pokročilého HL v posledních desetiletích tak odráží postupný přechod od prosté eskalace intenzity chemoterapie k individualizované léčbě založené na biologických charakteristikách onemocnění a hodnocení časně léčebné odpovědi.

V rámci léčby pokročilých stadií HL jsme byli GHSG přizváni ke spolupráci na projektu, jehož cílem bylo ověřit, zda zkrácení léčby z osmi na šest cyklů eskalovaného režimu BEACOPP s následnou PET-řízenou radioterapií umožní zachovat dlouhodobou účinnost léčby při současném snížení její kumulativní toxicity. Podrobnější výsledky a význam této léčebné strategie přinášejí následující publikace.

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Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial



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Summary

Background The intensity of chemotherapy and need for additional radiotherapy in patients with advanced stage Hodgkin's lymphoma has been unclear. We did a prospective randomised clinical trial comparing two reduced-intensity chemotherapy variants with our previous standard regimen. Chemotherapy was followed by PET-guided radiotherapy.

Methods In this parallel group, open-label, multicentre, non-inferiority trial (HD15), 2182 patients with newly diagnosed advanced stage Hodgkin's lymphoma aged 18–60 years were randomly assigned to receive either eight cycles of BEACOPP_{escalated} (8×B_{esc} group), six cycles of BEACOPP_{escalated} (6×B_{esc} group), or eight cycles of BEACOPP₁₄ (8×B₁₄ group). Randomisation (1:1:1) was done centrally by stratified minimisation. Non-inferiority of the primary endpoint, freedom from treatment failure, was assessed using repeated CIs for the hazard ratio (HR) according to the intention-to-treat principle. Patients with a persistent mass after chemotherapy measuring 2·5 cm or larger and positive on PET scan received additional radiotherapy with 30 Gy; the negative predictive value for tumour recurrence of PET at 12 months was an independent endpoint. This trial is registered with Current Controlled Trials, number ISRCTN32443041.

Findings Of the 2182 patients enrolled in the study, 2126 patients were included in the intention-to-treat analysis set, 705 in the 8×B_{esc} group, 711 in the 6×B_{esc} group, and 710 in the 8×B₁₄ group. Freedom from treatment failure was sequentially non-inferior for the 6×B_{esc} and 8×B₁₄ groups as compared with 8×B_{esc}. 5-year freedom from treatment failure rates were 84·4% (97·5% CI 81·0–87·7) for the 8×B_{esc} group, 89·3% (86·5–92·1) for 6×B_{esc} group, and 85·4% (82·1–88·7) for the 8×B₁₄ group (97·5% CI for difference between 6×B_{esc} and 8×B_{esc} was 0·5–9·3). Overall survival in the three groups was 91·9%, 95·3%, and 94·5% respectively, and was significantly better with 6×B_{esc} than with 8×B_{esc} (97·5% CI 0·2–6·5). The 8×B_{esc} group showed a higher mortality (7·5%) than the 6×B_{esc} (4·6%) and 8×B₁₄ (5·2%) groups, mainly due to differences in treatment-related events (2·1%, 0·8%, and 0·8%, respectively) and secondary malignancies (1·8%, 0·7%, and 1·1%, respectively). The negative predictive value for PET at 12 months was 94·1% (95% CI 92·1–96·1); and 225 (11%) of 2126 patients received additional radiotherapy.

Interpretation Treatment with six cycles of BEACOPP_{escalated} followed by PET-guided radiotherapy was more effective in terms of freedom from treatment failure and less toxic than eight cycles of the same chemotherapy regimen. Thus, six cycles of BEACOPP_{escalated} should be the treatment of choice for advanced stage Hodgkin's lymphoma. PET done after chemotherapy can guide the need for additional radiotherapy in this setting.

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Introduction

The introduction of multi-agent chemotherapy and improved radiation techniques has rendered Hodgkin's lymphoma one of the most favourable cancers in terms of likelihood of cure. Accordingly, the goal of most recent clinical trials in this malignancy has been to minimise intensity of treatment while maintaining previous levels of tumour control, particularly in early stage disease.^{1,2} An example is the German Hodgkin Study Group's (GHSG) HD10 study³ of patients with favourable limited stage disease, which showed that reduction in both

number of chemotherapy cycles and radiation dose was possible without loss of efficacy.

By contrast with the impressive cure rates in early stages, only 65–70% of patients diagnosed with advanced stage Hodgkin's lymphoma are disease-free at 5 years when treated with ABVD or similar chemotherapy.^{4,5} For more than 20 years of clinical research, attempts were made to improve on the efficacy of ABVD in this group of patients.^{6–8} The most promising regimens emerging were BEACOPP_{escalated}^{9,10} and Stanford-V.¹¹ However, results from randomised trials in advanced Hodgkin's lymphoma

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showed no benefit of Stanford-V over ABVD.^{12–14} By contrast, BEACOPP^{escalated} resulted in improved tumour control and overall survival in the GHSG HD9 study when compared with a variant of the ABVD regimen.^{9,10} Better tumour control as compared with ABVD was confirmed in two randomised trials.^{15,16}

Although clearly more effective, there has been some concern about the higher toxic effects of eight cycles of BEACOPP^{escalated} (8×B_{esc}) compared with ABVD. To reduce treatment-related toxic effects for patients with advanced stage Hodgkin's lymphoma, the GHSG did a follow-up study (HD15) comparing 8×B_{esc} with two less intensive regimens: six cycles of BEACOPP^{escalated} (6×B_{esc}) or eight cycles of a time intensified baseline-dose BEACOPP variant given in 14-day intervals (8×B₁₄).¹⁷ The primary objective of the trial presented here was to show non-inferiority of tumour control for the experimental groups. By contrast with previous studies in which radiotherapy was applied to initial bulky and residual disease, we assessed if radiotherapy given only to patients with a persistent mass measuring 2·5 cm or more, and positive on PET scan after chemotherapy, was adequate.

Methods

Study design and patients

HD15 was an unmasked, multicentre, randomised, group-sequential, non-inferiority trial for patients with advanced stage Hodgkin's lymphoma. Patients with newly diagnosed, histology-proven Hodgkin's lymphoma in Ann-Arbor stage IIB having large mediastinal mass (a third or more of the maximal thoracic diameter) or extranodal lesions, and all patients in stages III and IV

were recruited and treated in 408 hospitals and practices in Germany, the Czech Republic, Switzerland, The Netherlands, and Austria. Other inclusion criteria were an ECOG performance status of 2 or lower, age 18–60 years, HIV negativity, and freedom from concurrent disease. Histology done by the primary-care pathologist was re-assessed by at least one of a panel of six expert lymphoma pathologists. Details on inclusion, exclusion, and response criteria and definitions of endpoints are given in the appendix.

The trial was designed by the GHSG steering committee and approved by the ethics committees of participating centres. An independent data safety committee monitored patients' safety and efficacy of treatment throughout the 5-year study period.

Randomisation and masking

Patients were registered at the GHSG central head office by telephone and then centrally randomly assigned at an allocation ratio of 1:1:1 into one of the following treatment groups: eight cycles of BEACOPP^{escalated} (8×B_{esc} group), six cycles of BEACOPP^{escalated} (6×B_{esc} group), or eight cycles of BEACOPP₁₄ (8×B₁₄ group). Randomisation used the minimisation method including a random component and was stratified according to sex, participating centre, tumour stage (IIB or IIIA vs IIB or IV), age (<50 years vs ≥50 years), International Prognostic Score¹⁸ (IPS, <3 vs ≥3), and haemoglobin (<12 vs ≥12 g/dL). The minimisation algorithm was implemented in the study database with restricted access. Neither patients, investigators nor central head office personnel were masked to the treatment group chosen by the allocation procedure.

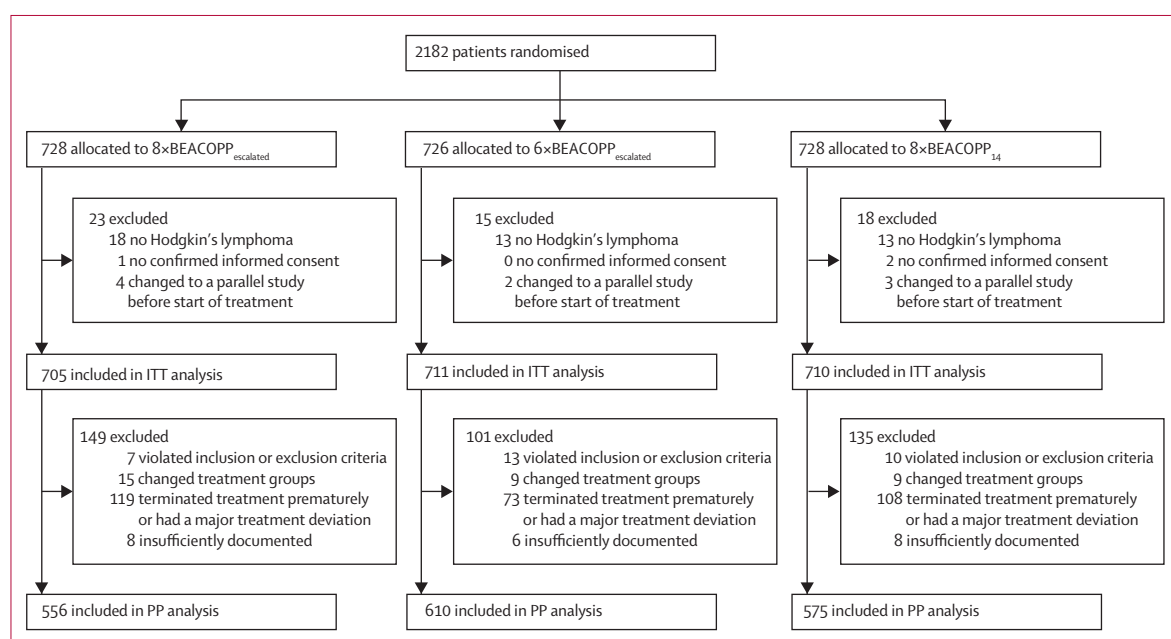


Figure 1: Trial profile

ITT=intention-to-treat. PP=per-protocol

Procedures

BEACOPP^{escalated} was given in 3-week intervals and BEACOPP₁₄ in baseline dose recycled every 2 weeks. Treatment administration has previously been reported^{9,17} and is described in the appendix, which includes predefined dose reduction rules. Response was assessed by CT scans of initially involved areas after four cycles and after the end of chemotherapy.

Entry criteria for the PET assessment in this trial were partial response after six to eight cycles of BEACOPP and at least one involved nodal site of 2.5 cm or larger in the transverse or longitudinal diameter as measured by CT. Exclusion criteria included diabetes mellitus, elevated fasting blood sugar level of more than 130 mg/dL, and skeletal involvement with risk of instability.

Recommended timing of ¹⁸F-fluorodeoxyglucose PET was at least 2 weeks after finishing the last BEACOPP course. A multidisciplinary panel consisting of experts from medical oncology, nuclear medicine, radiation oncology, radiology, and statistics reviewed PET and CT scans as well as conventional x-rays and clinical information. This central review panel also assessed inclusion and exclusion criteria for the PET objective and decided on residual disease being either PET-positive or PET-negative according to defined criteria.^{19,20}

Radiotherapy of 30 Gy was restricted to patients who had residual disease of 2.5 cm or more after chemotherapy and were PET-positive by central review panel decision. Radiotherapy was centrally planned and given in single fractions of 1.8–2.0 Gy five times weekly to PET-positive residual lesions.

Statistical analysis

The primary objective of this study was to show non-inferiority of two less intensive regimens with respect to the primary efficacy endpoint, freedom from treatment failure. Based on the HD9 trial, we assumed a 5-year freedom from treatment failure rate of 87% for the standard arm (8×B_{esc}); a maximum decrease of 6% in efficacy of the study groups was considered tolerable. This resulted in a non-inferiority margin of 1.51 for the hazard ratio (HR). Secondary endpoints were overall survival, progression-free survival, complete remission, and treatment-related toxic effects. The negative predictive value of PET was an independent endpoint in this trial. The trial was designed in parallel groups with five interim analyses (appendix).

We analysed the results using group sequential methods with CIs and p values for the primary endpoint adjusted according to the Pocock design using the repeated CI approach.²¹ We displayed time-to-event endpoints using the Kaplan-Meier method, and compared between groups using log-rank tests for p values, and univariate Cox regression for HRs. We analysed outcomes and toxic effects rates using the Fisher's exact test.

We calculated the negative predictive value in PET-negative patients as the proportion of patients without progression, relapse, or radiotherapy within 12 months

of the panel decision. We estimated the 95% CI for the negative predictive value using the normal approximation to the binomial distribution.

We tested our hypotheses according to the intention-to-treat principle and on a per-protocol analysis set (appendix). We considered a p value of less than 0.05 significant for single comparisons; in case of two

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See Online for appendix

	8×BEACOPP ^{escalated} (N=705)	6×BEACOPP ^{escalated} (N=711)	8×BEACOPP ₁₄ (N=710)
Age (years)			
Median (range)	33 (18–60)	34 (18–60)	33 (18–59)
18–19	48 (7%)	44 (6%)	41 (6%)
20–29	246 (35%)	221 (31%)	248 (35%)
30–39	180 (26%)	195 (27%)	191 (27%)
40–49	141 (20%)	154 (22%)	137 (19%)
50–60	90 (13%)	97 (14%)	93 (13%)
Sex			
Female	277 (39%)	280 (39%)	281 (40%)
Male	428 (61%)	431 (61%)	429 (60%)
B symptoms			
A	219 (31%)	258 (36%)	226 (32%)
B	486 (69%)	453 (64%)	484 (68%)
Ann Arbor stage*			
IIB	118 (17%)	104 (15%)	109 (15%)
IIIA	153 (22%)	178 (25%)	159 (22%)
IIIB	192 (27%)	179 (25%)	204 (29%)
IVA	65 (9%)	78 (11%)	67 (9%)
IVB	176 (25%)	170 (24%)	171 (24%)
ECOG performance status			
0	358 (51%)	369 (52%)	376 (53%)
1	316 (45%)	304 (43%)	301 (42%)
≥2	31 (4%)	38 (5%)	33 (5%)
Risk factors			
Large mediastinal mass†	210 (30%)	209 (29%)	212 (30%)
Extranodal involvement	136 (19%)	133 (19%)	143 (20%)
Involvement of ≥3 nodal areas	602 (85%)	597 (84%)	614 (86%)
High erythrocyte sedimentation rate‡	463 (66%)	448 (63%)	481 (68%)
IPS (grouped)			
0–1	222 (31%)	237 (33%)	223 (31%)
2–3	380 (54%)	367 (52%)	368 (52%)
4–7	103 (15%)	107 (15%)	119 (17%)
Reference histology (n=1829 [86%])			
Nodular sclerosis cHL	359/604 (59%)	350/618 (57%)	348/607 (57%)
Mixed cellularity cHL	147/604 (24%)	168/618 (27%)	135/607 (22%)
Lymphocyte-rich cHL	15/604 (2%)	13/618 (2%)	15/607 (2%)
Lymphocyte-depleted cHL	5/604 (1%)	3/618 (<1%)	7/607 (1%)
cHL, not further specified	57/604 (9%)	66/618 (11%)	76/607 (13%)
Nodular lymphocyte predominant Hodgkin's lymphoma	21/604 (3%)	18/618 (3%)	26/607 (4%)

Data are number (%) or n/N (%), unless otherwise indicated. ECOG=Eastern Cooperative Oncology Group.

IPS=International Prognostic Score. cHL=classical Hodgkin's lymphoma. *Three patients reclassified as stage IIA.

†≥1/3 of the maximum thoracic diameter as measured on chest radiography. ‡≥50 mm/h without B symptoms, ≥30 mm/h in case of B symptoms.

Table 1: Baseline characteristics by treatment group

	8×BEACOPP ^{escalated} (N=705)	6×BEACOPP ^{escalated} (N=711)	8×BEACOPP ₁₄ (N=710)
Acute toxicity (WHO grade 3 or 4)*			
At least one event	658/684 (96.2%)	671/696 (96.4%)	619/693 (89.3%)
Leucopenia	613/684 (89.6%)	619/696 (88.9%)	504/693 (72.7%)
Anaemia	425/684 (62.1%)	370/696 (53.2%)	385/693 (55.6%)
Thrombocytopenia	429/684 (62.7%)	372/696 (53.4%)	133/693 (19.2%)
Any haematological	632/684 (92.4%)	638/696 (91.7%)	552/693 (79.7%)
Alopecia	374/684 (54.7%)	368/696 (52.9%)	369/693 (53.2%)
Infection	169/684 (24.7%)	155/696 (22.3%)	143/693 (20.6%)
Nausea or vomiting	88/684 (12.9%)	77/696 (11.1%)	74/693 (10.7%)
Mucositis	83/684 (12.1%)	73/696 (10.5%)	55/693 (7.9%)
Pain	90/684 (13.2%)	64/696 (9.2%)	56/693 (8.1%)
Nervous system	52/684 (7.6%)	35/696 (5.0%)	88/693 (12.7%)
Respiratory tract	44/684 (6.4%)	26/696 (3.7%)	64/693 (9.2%)
Gastrointestinal tract	47/684 (6.9%)	44/696 (6.3%)	41/693 (5.9%)
Drug fever	30/684 (4.4%)	28/696 (4.0%)	31/693 (4.5%)
Secondary neoplasia			
Total	33 (4.7%)	17 (2.4%)	22 (3.1%)
sAML/MDS	19 (2.7%)	2 (0.3%)	8 (1.1%)
NHL	8 (1.1%)	6 (0.8%)	5 (0.7%)
Solid tumour	6 (0.9%)	9 (1.3%)	9 (1.3%)
Causes of death			
Total	53 (7.5%)	33 (4.6%)	37 (5.2%)
Hodgkin's lymphoma	13 (1.8%)	11 (1.5%)	15 (2.1%)
Treatment-related toxic effects	15 (2.1%)	6 (0.8%)	6 (0.8%)
Secondary neoplasia	13 (1.8%)	5 (0.7%)	8 (1.1%)
Toxic effects of salvage treatment	2 (0.3%)	2 (0.3%)	1 (0.1%)
Other†	6 (0.9%)	6 (0.8%)	4 (0.6%)
Unclear	4 (0.6%)	3 (0.4%)	3 (0.4%)

Data are number (%) or n/N (%). sAML=secondary acute myeloid leukaemia. MDS=myelodysplastic syndrome. NHL=non-Hodgkin's lymphoma. *Toxicities with an incidence of at least 3% only. †Suicide (n=3), cardiovascular (n=3), respiratory (n=2), accident (n=2), single reasons (n=6).

Table 2: Adverse events by treatment group

parallel tests (8×B_{esc} vs 6×B_{esc} and 8×B_{esc} vs 8×B₁₄), the significance level was 0.025. Preplanned subgroup analyses included sex, age, and risk groups according to IPS (0–1; 2–3; and 4–7).

This concluding analysis of the HD15 study is based on the fourth preplanned interim analysis. A separate analysis on the impact of erythropoietin has been published²² without touching any of the major questions reported here.

This trial is registered with Current Controlled Trials, number ISRCTN32443041.

Role of the funding source

The Deutsche Krebshilfe reviewed the trial protocol for adherence to good clinical practice. All financial supporters had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

2182 patients were randomly assigned to treatment groups between Jan 28, 2003, and April 18, 2008. 44 patients were excluded from all analyses since Hodgkin's lymphoma was not confirmed by reference histology (figure 1). Also excluded were nine patients who became part of a different study and three who withdrew their informed consent. Thus, the intention-to-treat analysis set included 2126 patients (705 assigned to the 8×B_{esc} group, 711 to the 6×B_{esc} group, and 710 to the 8×B₁₄ group). A total of 385 patients did not qualify for the per-protocol analysis that included 1741 patients (figure 1).

Table 1 summarises the baseline characteristics of patients included in this trial. The median age was 33 years (18–60); more patients were male and B-symptoms were present in two thirds of the patients. The most frequent subtype diagnosed by the pathology reference panel was nodular sclerosis followed by mixed cellularity. Treatment groups were well balanced for all characteristics shown (table 1).

Overall, most patients experienced at least one WHO toxic effect of grade 3 or 4 (table 2). Generally, patients in the 8×B_{esc} and 6×B_{esc} groups experienced more haematological events than did those in the 8×B₁₄ group. Leucopenia was observed in about 90% of patients in the 8×B_{esc} and 6×B_{esc} groups, and in about 70% of patients in the 8×B₁₄ group. Anaemia was documented for 57% of patients, with no apparent difference between groups. Thrombocytopenia was 2–3 times more frequent in the 8×B_{esc} and 6×B_{esc} groups than in the 8×B₁₄ group. Infections were observed in 23% (467 of 2073) of patients. Neurotoxic effects and pulmonary toxic effects were more frequent in the 8×B₁₄ group than in the 8×B_{esc} and 6×B_{esc} groups.

So far, 72 (3.4%) of 2126 patients have had secondary cancers (table 2), including 29 secondary acute myeloid leukaemias/myelodysplastic syndromes (sAML/MDS), 19 non-Hodgkin lymphomas, and 24 solid tumours. Patients in the 8×B_{esc} group had significantly more secondary cancers than did those in the 6×B_{esc} group (p=0.02). The number of sAML/MDS was 19 with 8×B_{esc}, two with 6×B_{esc} (p=0.0001), and eight with 8×B₁₄.

At a median follow-up of 48 months, 123 (6%) of 2126 patients had died (table 2); there were more deaths in the 8×B_{esc} group than in the 6×B_{esc} and 8×B₁₄ groups. The higher mortality in the 8×B_{esc} group was mainly due to differences in treatment-related events and secondary malignancies.

1961 (92%) of 2126 patients had complete remission with or without residual abnormalities (Fisher's exact test for three groups p=0.01; table 3).

5-year rates for the primary endpoint, freedom from treatment failure, were 84.4% in the 8×B_{esc} group, 89.3% in the 6×B_{esc} group, and 85.4% in the 8×B₁₄ group (table 3; figure 2A). In the primary sequential analysis, 6×B_{esc} and 8×B₁₄ treatments were non-inferior when compared with 8×B_{esc} with both 97.5% repeated CIs for the HR excluding

the non-inferiority margin of 1.51 ($6\times B_{esc}$ vs $8\times B_{esc}$, 0.44 to 1.02; $8\times B_{14}$ vs $8\times B_{esc}$, 0.62 to 1.36; appendix). Thus, the study objective of showing non-inferiority for freedom from treatment failure was achieved for both experimental treatments. When $8\times B_{esc}$ was directly compared with $6\times B_{esc}$, freedom from treatment failure did not significantly differ in the sequential analysis ($p=0.037$) but it did significantly differ in the descriptive non-sequential analysis (log-rank $p=0.009$; table 3); the difference between $8\times B_{esc}$ and $8\times B_{14}$ was not significant (log-rank $p=0.5$; table 3). The better efficacy of $6\times B_{esc}$ had been present in all three previous interim analyses. The results were very similar for progression-free survival (table 3). The sequential analysis was confirmed when those patients violating inclusion or exclusion criteria were excluded.

A post-hoc analysis of time-to-progression explored differences in freedom from treatment failure and progression-free survival between groups. In particular, $8\times B_{14}$ treatment was less effective in inducing lasting remissions than $6\times B_{esc}$ treatment (5-year time to progression 87.7% vs 92.6%; $p=0.016$). The 5-year time to progression for $8\times B_{esc}$ treatment was 89.9% (figure 2B).

Overall survival in the intention-to-treat population was significantly higher in the $6\times B_{esc}$ group than in the $8\times B_{esc}$ group (table 3, figure 2C); whereas it did not differ between $8\times B_{esc}$ and $8\times B_{14}$ groups (table 3).

Subgroup analyses by sex, age, and IPS showed that $6\times B_{esc}$ consistently outperformed $8\times B_{esc}$ (data not shown). Results for freedom from treatment failure, progression-free survival, and overall survival were confirmed in the supplementary per-protocol analysis with larger absolute differences compared with the intention-to-treat analysis (table 4). Of note, $6\times B_{esc}$ was superior to $8\times B_{14}$ at 5 years in terms of freedom from treatment failure and progression-free survival (table 4).

The central PET review panel assessed 822 (39%) of 2126 patients in the intention-to-treat set of whom 739 were qualified (AS-PET; appendix). 28 of these patients had no documented follow-up of at least 12 months. Thus, 711 patients qualified for the assessment of the negative predictive value of PET (AS-NPV).

In 739 qualified patients with a persistent mass measuring 2.5 cm or more, PET was positive in 191 (26%, 49 [22%] of 226 patients in the $8\times B_{esc}$ group, 74 [30%] of 249 patients in the $6\times B_{esc}$ group, and 68 [26%] of 264 patients in the $8\times B_{14}$ group). Protocol adherence was good with 540 (99%) of 548 PET-negative patients not receiving radiotherapy and 175 (92%) of 191 PET-positive patients receiving radiotherapy. More patients in the $6\times B_{esc}$ and $8\times B_{14}$ groups than in the $8\times B_{esc}$ group had PET-positive residues after the end of chemotherapy and therefore received additional radiotherapy (63 [9%] of 705 patients in the $8\times B_{esc}$ group vs 86 [12%] of 711 patients in the $6\times B_{esc}$ group vs 76 [11%] of 710 patients in the $8\times B_{14}$ group, Fisher's exact test for the three groups $p=0.15$).

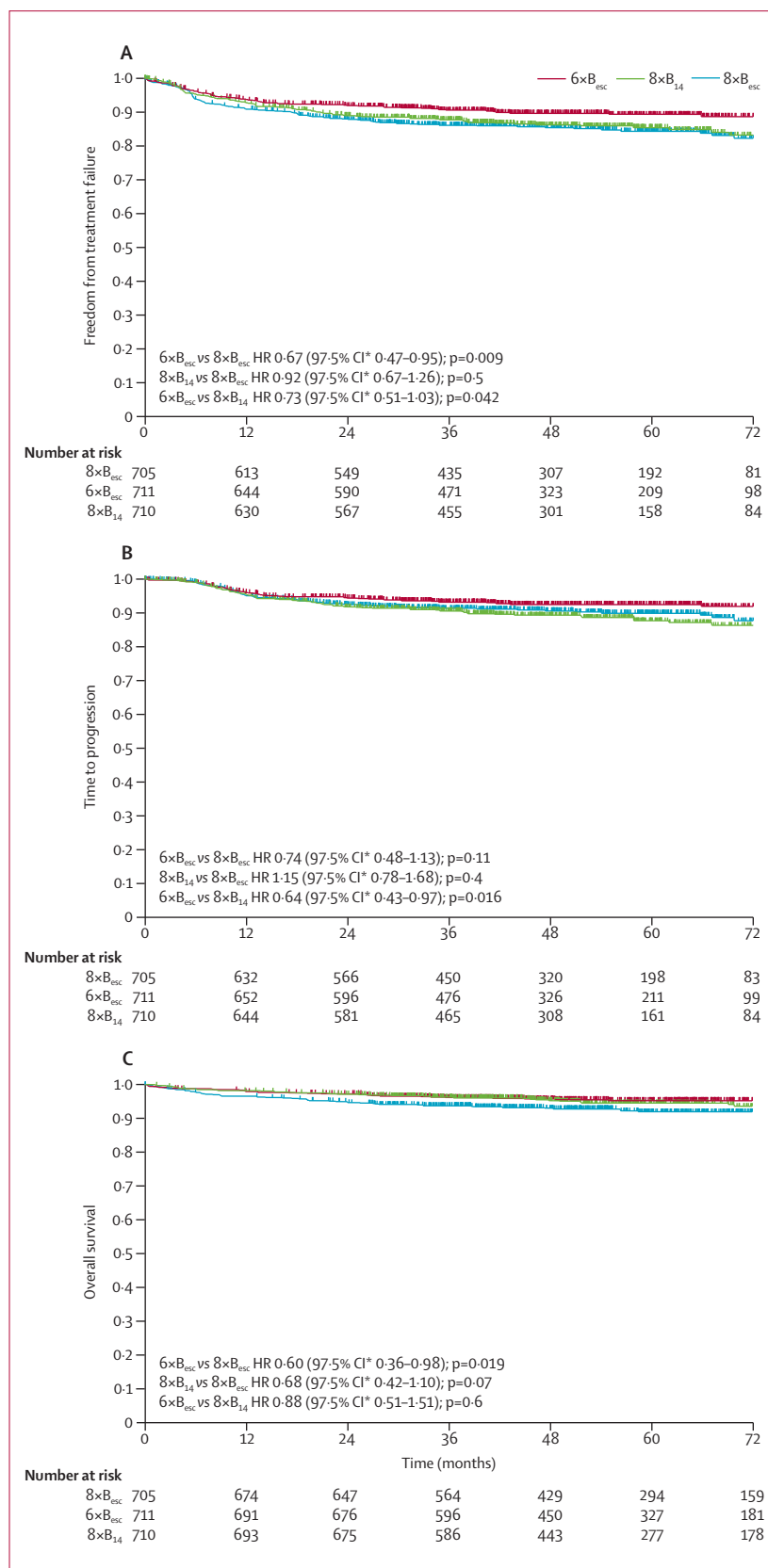
	8×BEACOPP ^{escalated} (N=705)	6×BEACOPP ^{escalated} (N=711)	8×BEACOPP ₁₄ (N=710)
Final response*			
Complete remission with or without residual abnormalities	635 (90.1%)	670 (94.2%)	656 (92.4%)
Partial remission	18 (2.6%)	9 (1.3%)	14 (2.0%)
Progression	16 (2.3%)	13 (1.8%)	17 (2.4%)
No change	3 (0.4%)	0	0
Unknown	33 (4.7%)	19 (2.7%)	23 (3.2%)
Survival rate			
5-year freedom from treatment failure	84.4 (81.0 to 87.7)	89.3 (86.5 to 92.1)	85.4 (82.1 to 88.7)
Difference from 8×BEACOPP ^{escalated}	NA	4.9 (0.5 to 9.3)	1.1 (−3.7 to 5.8)
Difference from 6×BEACOPP ^{escalated}	NA	NA	−3.9 (−8.2 to 0.5)
5-year progression-free survival	85.6 (82.3 to 88.9)	90.3 (87.6 to 93.0)	85.8 (82.4 to 89.2)
Difference from 8×BEACOPP ^{escalated}	NA	4.7 (0.4 to 8.9)	0.2 (−4.5 to 5.0)
Difference from 6×BEACOPP ^{escalated}	NA	NA	−4.5 (−8.9 to −0.1)
5-year overall survival	91.9 (89.4 to 94.4)	95.3 (93.4 to 97.2)	94.5 (92.5 to 96.6)
Difference from 8×BEACOPP ^{escalated}	NA	3.3 (0.2 to 6.5)	2.6 (−0.6 to 5.9)
Difference from 6×BEACOPP ^{escalated}	NA	NA	−0.7 (−3.5 to 2.1)

Data are number (%) or % (97.5% CI). NA=not applicable. *Defined as the status of Hodgkin's lymphoma at the final restaging after end of primary treatment including radiotherapy if given. If the patient does not have a complete remission, no further treatment is given, and there is no progression of disease within 6 months, the final response is retrospectively redefined as complete remission with residual abnormalities.

Table 3: Efficacy outcomes by treatment group

24 (4.5%) of 529 PET-negative patients with a follow-up of at least 12 months had progression or relapse within 12 months of the PET panel decision (appendix). Eight patients received additional radiotherapy against panel recommendation of whom seven had no recurrence in the predefined 12 months of follow-up, but counted as failures for the negative predictive value. Thus, there were a total of 31 failures resulting in a negative predictive value of 94.1% at 12 months (95% CI 92.1–96.1). This conservative calculation is above the predefined lower threshold of 90%. Recurrence in seven of the 24 patients with progression or relapse was confined to residual tissue sites only, whereas the other 17 cases also had lesions outside the residual mass. Within 12 months of follow-up, 20 (11%) of the 182 PET-positive patients had progressive disease ($n=18$) or early relapse ($n=2$).

Figure 3 shows progression-free survival of PET-negative and PET-positive patients. Progression-free survival for PET-negative or PET-positive patients was 92.6% and 86.2% at 48 months (95% CI for difference 0.9–12.0, log-rank $p=0.022$). Thus, a positive PET after effective chemotherapy was associated with higher risk of subsequent treatment failure, even though PET-positive patients were treated with additional radiotherapy and PET-negative patients were not. Progression-free survival of PET-negative and PET-positive patients having partial remission with 2.5 cm or larger residual disease was also compared with that of patients in complete remission after completing chemotherapy (figure 3).



This analysis showed that patients in partial remission with a PET-negative persistent mass after chemotherapy had a prognosis very similar to those in complete remission as measured by conventional CT (4-year progression-free survival of 92.1%).

Discussion

The goal of the three-arm HD15 study presented here was to reduce toxic effects of treatment while maintaining efficacy in patients with advanced stage Hodgkin's lymphoma. The primary endpoint in this trial, non-inferiority in terms of freedom from treatment failure, was clearly proven for 6xBeacopp and 8xBeacopp groups 3 years ahead of the planned final analysis. When freedom from treatment failure was compared between 8xBeacopp and 6xBeacopp groups, it did not differ in the sequential analysis but did, significantly, in the descriptive non-sequential analysis. For all secondary endpoints in this trial, the comparison significantly favoured 6xBeacopp treatment. Freedom from treatment failure for patients receiving 8xBeacopp was also non-inferior to that of those receiving 8xBeacopp. Compared with 8xBeacopp escalated, 6xBeacopp was associated with less treatment-related mortality and significantly fewer secondary cancers. Overall, 6xBeacopp showed better efficacy and fewer serious toxic effects than 8xBeacopp.

In the previous GHSG HD9 trial,¹⁰ treatment with 8xBeacopp was 18% better in freedom from treatment failure and 11% in overall survival at 10 years than an ABVD variant. Results from two Italian studies^{15,16} showed clear advantage in tumour control but no difference in overall survival when comparing ABVD with four cycles BEACOPP escalated followed either by two or four additional cycles of BEACOPP given in baseline dose (panel). However, these studies had small patient numbers and were not sufficiently powered to detect differences in overall survival.

Another direct comparison between ABVD and BEACOPP escalated was done by the European Organisation for Research and Treatment of Cancer (EORTC) and Groupe d'Etude des Lymphomes de l'Adulte (GELA; ClinicalTrials.gov, NCT00049595). Although the final results are not available yet, it is noteworthy that both groups have adopted BEACOPP escalated as the standard in their independent trials for advanced stage Hodgkin's lymphoma (ClinicalTrials.gov, NCT01358747). The fact that treatment with 6xBeacopp in the present HD15 trial was less toxic, and more effective, than eight cycles will very probably result in more frequent use of this regimen. Treatment-related mortality in those patients receiving six cycles was less than 1% in a setting with 408 study centres from five European countries including all levels of care. This indicates that six cycles of BEACOPP escalated

Figure 2: Kaplan-Meier estimates for chemotherapy objective
 (A) Freedom from treatment failure. (B) Time to progression.
 (C) Overall survival. 8xBeacopp=8xBeacopp escalated; 6xBeacopp=6xBeacopp escalated;
 8xBeacopp escalated=8xBeacopp escalated. *non-sequential CIs.

are safe and more widely applicable. Groups having no experience with this treatment need to follow the pre-defined guidelines for dose reduction of BEACOPP^{escalated} to avoid unnecessary toxic effects.

The role of PET-guided radiotherapy after chemotherapy was another endpoint in the present study. Several small non-randomised trials^{24–27} had raised interest in PET as a possible prognostic tool in patients with Hodgkin's lymphoma. Currently ongoing studies randomly assigning patients between standard treatment and PET-based response-adapted approaches should shed more light on this strategy. So far, however, there are very few data on PET-guided additional radiotherapy after chemotherapy in advanced Hodgkin's lymphoma.²⁸ The negative predictive value of PET in the present study data confirms the previous interim analysis based on the first 311 patients and shorter follow-up.²⁹ Patients who were in PET-negative partial remission after chemotherapy had a prognosis very similar to that of patients who were in complete remission as measured by conventional CT. Our data suggest that PET can indeed identify non-active Hodgkin's lymphoma and are thus formal proof for the introduction of PET into the revised response assessment criteria for malignant lymphoma in which patients in PET-negative partial remission qualify as being in complete remission.²⁰

Additional radiotherapy after chemotherapy in advanced stage Hodgkin's lymphoma is associated with higher long-term toxic effects and its role has been a matter of debate.³⁰ Recent studies^{31,32} suggested that only those patients with Hodgkin's lymphoma in advanced stages with residual disease after chemotherapy might need additional radiotherapy. With PET-guided assessment of residual disease after chemotherapy, the number of patients actually receiving additional radiotherapy after eight cycles of BEACOPP^{escalated} was reduced from 71% in the previous HD9 study to 11% in the present study. The outcome of patients in PET-negative partial remission was similar to those in complete remission with or without residual abnormalities after chemotherapy, suggesting that radiotherapy can be omitted in patients in PET-negative partial remission without loss of efficacy. Secondary solid tumours are at least partly associated with radiotherapy^{30,33} so that the lower number of patients receiving additional radiotherapy in the present trial should result in fewer solid tumours with longer follow-up. However, we need to be careful in extrapolating the PET-guided approach presented here to weaker regimens that might need more vigorous additional radiotherapy.

The present trial had some limitations: since the use of PET-guided radiotherapy was not assessed in a randomised fashion, we cannot distinguish between the effects of chemotherapy and radiotherapy on tumour control. A randomised assessment of the PET-guided radiotherapy approach would have yielded stronger evidence but was not pursued. Additionally, we did not clearly show the need for additional radiotherapy since biopsies of PET-positive tissue were not done. The rather

	8×BEACOPP ^{escalated} (N=556)	6×BEACOPP ^{escalated} (N=610)	8×BEACOPP ¹⁴ (N=575)
5-year freedom from treatment failure	84.9 (81.2 to 88.6)	90.8 (88.1 to 93.6)	86.0 (82.4 to 89.6)
Difference from 8×BEACOPP ^{escalated}	NA	5.9 (1.3 to 10.6)	1.1 (−4.1 to 6.3)
Difference from 6×BEACOPP ^{escalated}	NA	NA	−4.8 (−9.4 to −0.3)
5-year progression-free survival	85.3 (81.7 to 89.0)	91.1 (88.4 to 93.8)	86.4 (82.8 to 90.0)
Difference from 8×BEACOPP ^{escalated}	NA	5.8 (1.2 to 10.4)	1.1 (−4.1 to 6.2)
Difference from 6×BEACOPP ^{escalated}	NA	NA	−4.7 (−9.2 to −0.2)
5-year overall survival	91.8 (89.0 to 94.6)	96.2 (94.4 to 98.0)	94.8 (92.6 to 97.0)
Difference from 8×BEACOPP ^{escalated}	NA	4.4 (1.1 to 7.7)	3.0 (−0.5 to 6.6)
Difference from 6×BEACOPP ^{escalated}	NA	NA	−1.4 (−4.2 to 1.5)

Data are % (97.5% CI). NA=not applicable.

Table 4: Survival rate by treatment group (per-protocol analysis set)

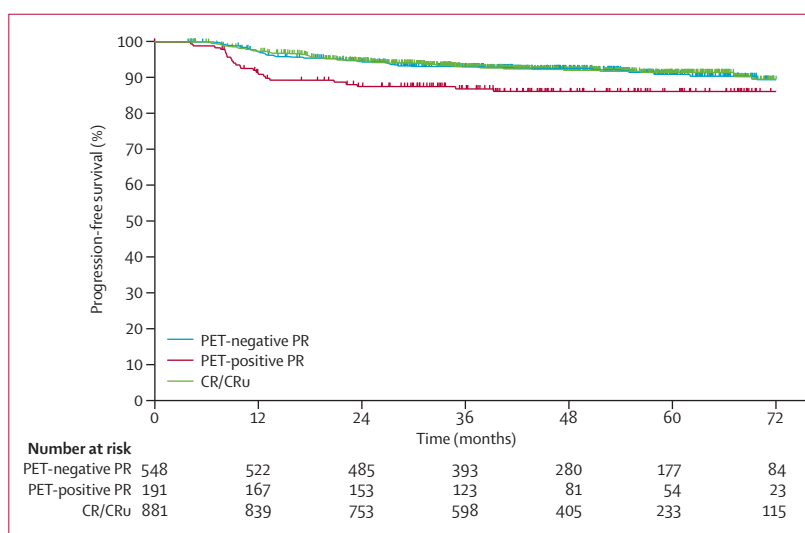


Figure 3: Progression free survival for PET study objective

PR=partial remission at the end of chemotherapy. CR/CRu=complete remission without or with residual abnormalities at the end of chemotherapy.

short follow-up limits the data on long-term side-effects in this trial.

At a median follow-up of 48 months, 72 secondary cancers (3%) were reported in this trial. This result compares favourably with data reported for BEACOPP in our previous HD9 and HD12 trials^{9,32} in advanced stage Hodgkin's lymphoma and is similar to the 3.0–3.4% previously reported for ABVD or Stanford V.¹⁴ Particularly, the induction of sAML/MDS associated with combined modality treatment in advanced stage Hodgkin's lymphoma is a general concern. In the present trial, more patients treated with 8×B_{esc} were diagnosed with sAML/MDS than were those treated with 6×B_{esc} or 8×B₁₄. Although these findings must be viewed with caution due to very small numbers, this difference could partly relate to threshold doses, particularly for cyclophosphamide and procarbazine.^{34,35} Here, the total overall dose for patients receiving 8×B_{esc} was 10 000 mg/m² of cyclophosphamide and 5600 mg/m²

Panel: Research in context

Systematic review

We searched Medline and the Cochrane Library without language restrictions up to Sept 30, 2011, for full papers reporting randomised controlled trials, systematic reviews, or meta-analyses in adults, with the search terms "Hodgkin*", "lymphoma", "advanced", and "chemotherapy". We excluded papers reporting on non-Hodgkin's lymphoma. The search identified three meta-analyses (appendix). Of 115 publications reporting randomised trials, 54 compared at least two chemotherapy regimens, and 29 publications studied chemotherapy-regimens containing ABVD or BEACOPP (appendix).

Six to eight cycles of ABVD is the most frequently used chemotherapy for the treatment of advanced stage Hodgkin's lymphoma in many countries. Within the GHSG and many European countries, eight cycles of BEACOPP^{escalated} plus involved field radiotherapy of residual tumour has become the standard treatment. A recently published randomised trial¹⁶ confirmed better freedom from first progression with eight cycles of BEACOPP compared with six to eight cycles of ABVD. The most recent meta-analysis similarly found superior progression-free survival for BEACOPP^{escalated} when compared with regimens containing ABVD.²³ However, eight cycles of BEACOPP^{escalated} are more toxic and the benefit for overall survival is still being debated.^{16,23}

Interpretation

In the HD15 study presented here, we found better overall survival, superior tumour control, and less toxicity with 6 cycles of BEACOPP^{escalated} as compared with eight cycles for treatment of advanced stage Hodgkin's lymphoma. Since the data presented here were generated by a large number of contributing centres from all levels of care, the results of HD15 should help reducing barriers against the use of this effective treatment in advanced stage Hodgkin lymphoma.

of procarbazine as compared with 7500 mg/m² and 4200 mg/m², respectively, for 6×B_{esc}.

In summary, the present study shows that in patients with advanced stage Hodgkin's lymphoma, six cycles of BEACOPP^{escalated} are better than eight cycles in terms of disease control and overall survival while being less toxic. Additionally, the use of PET after chemotherapy allowed restriction of additional radiotherapy to a few patients. Due to the better outcome and tolerability, 6×B_{esc} followed by PET-guided radiotherapy to residual disease is the new standard-of-care for advanced-stage Hodgkin's lymphoma in our practice.

Contributors

JM, CR, AH, JZ, ZK, MH, LK, HD, BD, NE, MT, SK, HA, AB, RK, CK, OS, RG, RA, MK, and MP directed clinical activities at participating study centres. HS coordinated the reference pathology. CK, MD, HTE, R-PM, and MF conducted the central PET review. HH led the statistical analyses of the data. MF directed activities at the GHSG central head office. AE, VD, and PB led the design of the study protocol. AE wrote the first draft of the report and was supported by HH; all authors contributed to data interpretation, reviewed the draft, and approved the final version of this report.

Conflicts of interest

We declare that we have no conflicts of interest.

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Preliminary results of the PET objective of the trial were partly presented at the 52nd American Society of Hematology (ASH) Annual Meeting and Exposition, Orlando, FL, USA, on Dec 4–7, 2010, and at the 2011 American Society of Clinical Oncology Annual Meeting, Chicago, IL, USA, on June 3–7, 2011. Results of the chemotherapy objective were presented at the 53rd ASH Annual Meeting and Exposition, San Diego, CA, USA, on Dec 10–13, 2011.

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Reduced-Intensity Chemotherapy in Patients With Advanced-Stage Hodgkin Lymphoma

Updated Results of the Open-Label, International, Randomised Phase 3 HD15 Trial by the German Hodgkin Study Group

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Abstract

The international, randomized phase 3 HD15 trial established 6xeBEACOPP as standard therapy for patients with newly diagnosed advanced-stage Hodgkin lymphoma (HL) within the German Hodgkin Study Group (GHSG). We performed a follow-up analysis to assess long-term efficacy and safety of this approach. Between 2003 and 2008, 2182 patients aged 18 to 60 years were recruited and randomized in a 1:1:1 ratio between 8 or 6 cycles of eBEACOPP or 8 cycles of the dose-dense BEACOPP-14 regimen, each followed by 30 Gy radiotherapy in case of positron emission tomography (PET)-positive residual lesions ≥ 2.5 cm. The study aimed at demonstrating non-inferiority regarding efficacy of the 2 experimental arms on a significance level of 2.5% each. The intention-to-treat analysis comprised 2126 patients with a median follow-up of 102 months. Ten-year progression-free survival was 81% (97.5% CI 77–85) with 8xeBEACOPP, 84% (80–87) with 6xeBEACOPP, and 84% (80–87) with 8xBEACOPP-14; the non-inferiority margin of 1.51 for the hazard ratio (HR) could be excluded for both comparisons (6xeBEACOPP, HR=0.7, 97.5% CI 0.5–1.0; 8xBEACOPP-14, HR=0.9, 97.5% CI 0.7–1.2). Overall survival at 10 years was 88% (85–91), 90% (88–93), and 92% (89–94), respectively. A total of 142 second malignancies corresponding to 10-year cumulative incidences of 10%, 7%, and 7% and standardized incidence ratios of 4.3, 2.5, and 2.8 were reported for 8xeBEACOPP, 6xeBEACOPP, and 8xBEACOPP-14, respectively. This updated analysis of the HD15 trial thus confirms the efficacy and reports on the long-term safety of a shortened first-line chemotherapy consisting of 6xeBEACOPP followed by PET-guided radiotherapy in advanced-stage HL.

Keywords: Advanced stages, Hodgkin lymphoma, long-term outcome

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Trial registration: The HD15 trial was registered with Current Controlled Trials, number ISRCTN32443041.

Author contributions: AE, JM, TP, JM, JMZ, ZK, DAE, MS and RG directed clinical activities at participating study centers. HS led the reference pathology. HE, CK, MD and MF did the central PET review. HG led the statistical analyses of the data. MF directed activities at the GHSG central office. AE, VD, and PB led the design of the study protocol. AE is the principal investigator of the study. AE and HG wrote the first draft of the report. All authors contributed to data interpretation, reviewed the draft, and approved the final version of this report.

Disclosure: The Deutsche Krebshilfe reviewed the trial protocol for adherence to good clinical practice. The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data and the corresponding author had final responsibility for the decision to submit for publication. The authors have indicated they have no potential conflicts of interest to disclose.

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Introduction

The prognosis of patients with Hodgkin lymphoma (HL) has improved with the introduction of multiagent chemotherapy such as MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) or ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), resulting in a 5-year tumor control of about 65% and an overall survival of 75% at 5 years.^{1,2} In an attempt to further improve the prognosis of this patient cohort, the German Hodgkin Study Group (GHSG) developed a more intensive protocol termed escalated BEACOPP (eBEACOPP; bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated dose). In the randomized HD9 trial, this regimen was compared with the GHSG standard at that time, 8xCOPP/ABVD (cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, dacarbazine), and a lower intensity BEACOPP variant termed baseline BEACOPP (bBEACOPP). Freedom from treatment failure (FFTF) at 5 years was 69% for COPP/ABVD, 76% for bBEACOPP, and 87% for eBEACOPP, respectively.³ Consequently, 8 cycles of eBEACOPP were established as standard of care for advanced-stage HL in the following GHSG trial HD12.⁴ In this trial, a dose reduction to 4 cycles of eBEACOPP followed by 4 cycles of bBEACOPP did not result in a meaningful reduction of treatment-associated toxicity. The subsequent randomized phase 3 HD15 trial showed the noninferiority of 6 cycles of eBEACOPP in terms of tumor control as compared to 8 cycles of eBEACOPP, with 5-year FFTF of 89% and 84%, respectively.⁵ As a consequence of HD15, the GHSG standard of care for advanced-stage HL changed to 6 cycles of eBEACOPP followed by positron emission tomography (PET)-guided radiotherapy. The original report of the HD15 trial had a

median follow-up of 48 months with 2126 patients included. To better understand the long-term outcomes and late side effects of treatment, we performed an update analysis on HD15 with substantially longer follow-up of 102 months.

Material and methods

Study design and patients

This open-label, multicenter, international, randomized phase 3 non-inferiority trial was conducted in more than 400 hospitals and private practices in Germany, the Czech Republic, Switzerland, the Netherlands, and Austria. We recruited patients aged 18 to 60 years with newly diagnosed, histology-proven, classical, or nodular lymphocyte-predominant HL in advanced stages (ie, clinical stage III-IV or stage II with B symptoms and 1 or both risk factors of large mediastinal mass [$\geq 1/3$ of the maximal thoracic diameter] or extranodal lesions). All patients provided written informed consent before study entry according to the Good Clinical Practice guidelines of the International Conference on Harmonisation and national regulations. The trial was designed by the GHSG steering committee, approved by the ethics committees of all participating countries and centers, and registered with Current Controlled Trials (IRCTN32443041).

Patients were randomly assigned to receive either 8 cycles of eBEACOPP, 6 cycles of eBEACOPP, or 8 cycles of the more dose-dense BEACOPP-14 in a 1:1:1 ratio. In all 3 groups, radiotherapy was recommended in case of lesions of at least 2.5 cm in the largest diameter with residual FDG uptake after chemotherapy. Follow-up examinations were performed and documented at increasing intervals after therapy completion, with computed

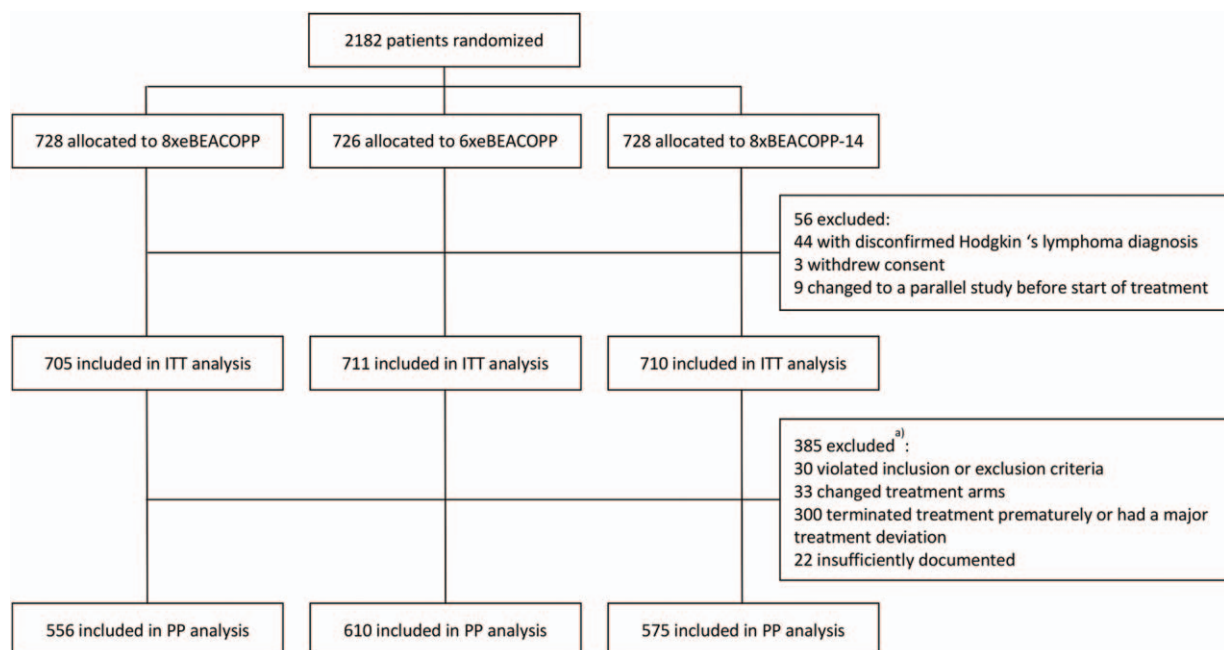


Figure 1. Trial profile. ITT is defined as the set of all patients except for those with disconfirmed diagnosis of Hodgkin lymphoma, withdrawal of consent or revision of staging and participation in another study before start of treatment. PP contains all ITT patients without severe protocol deviation, having complete therapy documentation or progressive disease or death during therapy. BEACOPP-14 = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in dose-dense variant, eBEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated dose, ITT = intention-to-treat, PP = per-protocol. (a) Analysis set definition based on data from final analysis.

tomography only performed at the investigators' discretion. Relapse of HL or occurrence of a second malignancy was confirmed by biopsy locally, and reports were verified by GHSG trial physicians before database entry. Details of inclusion criteria, procedures and statistics as well as final results of the trial have been published.⁵

Statistical analysis

In order to assess long-term treatment outcome, we used progression-free survival (PFS), defined as the time from completion of staging until progressive disease, relapse, or death from any cause. If none of these events had occurred, PFS was censored at the date of last information on the disease status. Overall survival was defined as time from completion of staging until death from any cause, or censored at the date of last information on the patient being alive. In cases of an information lag of more than 1 year, information on survival status was obtained from residents' registration offices wherever possible. To assess the long-term outcome of patients with progression or relapse, within this subgroup we report second PFS, defined as time from first progression or relapse to further relapse or death

from any cause, or censored at the date of last information on the disease status. Survival outcomes were analyzed according to Kaplan-Meier and compared between treatment groups using hazard ratios (HR) with CIs obtained from Cox regression models, whereby models for PFS and overall survival were adjusted for the stratification factors age (<50 years vs ≥50 years), sex, Ann Arbor stage (IIB or IIIA vs IIIB or IV), international prognostic score (IPS, <3 vs ≥3) and hemoglobin level (>12 vs ≤12 g/dL). Cumulative incidences of second malignancies were estimated according to Kaplan-Meier accounting for death as a competing risk, and compared between treatment groups using subdistribution Hazard Ratios (sHR) and CIs obtained from Cox regression models. We estimated standardized incidence ratios (SIR) for second malignancies by dividing observed by expected event numbers with respect to age- and sex-specific reference values for the German population,⁶ taking into account the observed person years in each sex/age group throughout the total study and follow-up period. Standardized mortality ratios (SMR) were estimated accordingly.⁷ In addition, we restricted mortality analyses to the long-term follow-up period starting 5 years after first diagnosis (SMR_{long-term}), including only patients having survived and being observed for at least 5 years. Patient

Table 1
Baseline Characteristics of the Intention-to-Treat Set

	8xeBEACOPP (N = 705)	6xeBEACOPP (N = 711)	8xBEACOPP-14 (N = 710)	Total (N = 2126)
Age				
Median (range)	33 (18–60)	34 (18–60)	33 (18–60)	33 (18–60)
Sex				
Female	277 (39%)	280 (39%)	281 (40%)	838 (39%)
Male	428 (61%)	431 (61%)	429 (60%)	1288 (61%)
Ann Arbor stage				
IIA*	1 (<1%)	2 (<1%)	0	3 (<1%)
IIB	118 (17%)	104 (15%)	109 (15%)	331 (16%)
IIIA	153 (22%)	178 (25%)	159 (22%)	490 (23%)
IIIB	192 (27%)	179 (25%)	204 (29%)	575 (27%)
IVA	65 (9%)	78 (11%)	67 (9%)	210 (10%)
IVB	176 (25%)	170 (24%)	171 (24%)	517 (24%)
GHSG risk factors				
Large mediastinal mass	210 (30%)	209 (29%)	212 (30%)	631 (30%)
Extranodal involvement	136 (19%)	133 (19%)	143 (20%)	412 (19%)
Involvement of 3 or more nodal areas	602 (85%)	597 (84%)	614 (87%)	1813 (85%)
Elevated erythrocyte sedimentation rate	463 (66%)	448 (63%)	481 (68%)	1392 (65%)
ECOG performance status				
0	358 (51%)	369 (52%)	376 (53%)	1103 (52%)
1	316 (45%)	304 (43%)	301 (42%)	921 (43%)
2	30 (4%)	37 (5%)	33 (5%)	100 (5%)
3*	1 (<1%)	1 (<1%)	0	2 (<1%)
IPS				
0–1	222 (31%)	237 (33%)	223 (31%)	682 (32%)
2–3	380 (54%)	367 (52%)	368 (52%)	1115 (52%)
4–7	103 (15%)	107 (15%)	119 (17%)	329 (15%)
Histologic subtype				
Nodular sclerosis cHL	367/614 (60%)	356/628 (57%)	353/616 (57%)	1076/1858 (58%)
Mixed cellularity cHL	147/614 (24%)	170/628 (27%)	138/616 (22%)	455/1858 (24%)
Lymphocyte-rich cHL	15/614 (2%)	13/628 (2%)	16/616 (3%)	44/1858 (2%)
Lymphocyte-depleted cHL	5/614 (1%)	3/628 (<1%)	7/616 (1%)	15/1858 (1%)
cHL, not further specified	59/614 (10%)	67/628 (11%)	76/616 (12%)	202/1858 (11%)
Nodular lymphocyte predominant HL	21/614 (3%)	19/628 (3%)	26/616 (4%)	66/1858 (4%)

Data are n (%) or n/total (%), unless otherwise indicated.

eBEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated dose. BEACOPP-14 = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in dose-dense variant. GHSG = German Hodgkin Study Group. ECOG = Eastern Cooperative Oncology Group. IPS = International Prognostic Score. cHL = classical Hodgkin lymphoma.

* Violation of inclusion criteria detected after study entry.

characteristics were analyzed descriptively. All analyses were performed according to the intention-to-treat (ITT) principle and on a per-protocol analysis set, which was based on data from the final analysis. The significance level was set to 5% for single comparisons and adjusted to 2.5% in case of 2 parallel tests (8xeBEACOPP vs 6xeBEACOPP and 8xeBEACOPP vs 8xBEACOPP-14). We used SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) for all analyses.

Results

Out of 2182 patients enrolled between January 28, 2003 and April 18, 2008, 56 were excluded from the ITT analysis due to disconfirmation of their HL diagnosis ($n=44$), withdrawal of consent ($n=3$) or revision of staging and participation in another study before start of treatment ($n=9$), resulting in 2126 patients finally analyzed (Fig. 1). Baseline characteristics are presented in

Table 1 and were similar between randomized treatment groups. The median age was 33 years (range 18–60), 61% were male, and 84% had stage III or IV disease.

Among 1987 patients who were alive at the time of the last analysis published in 2012, updated follow-up information was available for 89%. The last information was obtained from residents' registries in 17% of patients. Median follow-up was 112 months for survival and 102 months for disease status, respectively, and did not differ between trial arms.

With 10-year PFS estimates of 81% (97.5% CI 77%–85%), 84% (80%–87%), and 84% (80%–87%) for 8xeBEACOPP, 6xeBEACOPP, and 8xBEACOPP-14, respectively, noninferiority of both experimental treatment regimens could be confirmed with longer follow-up (Fig. 2A): the HR and respective 97.5% CI were 0.7 (0.5–1.01) for 6xeBEACOPP and 0.9 (0.7–1.2) for 8xBEACOPP-14, respectively, versus 8xeBEACOPP, and both excluded the noninferiority margin of 1.51. In the per-protocol

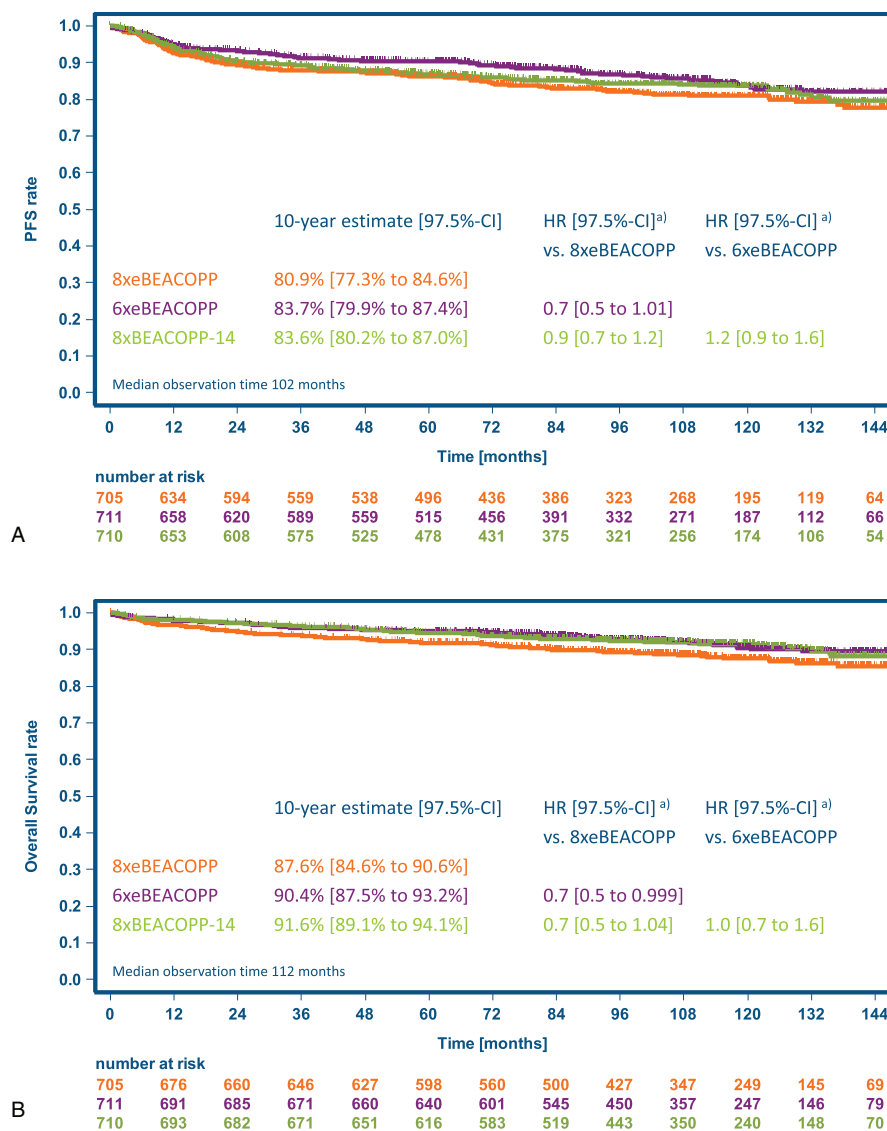


Figure 2. Kaplan-Meier estimates for the intention-to-treat set. (A) Progression-free survival. (B) Overall survival. BEACOPP-14=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in dose-dense variant, eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated dose, HR=hazard ratio, PFS=progression-free survival. (a) Hazard ratios adjusted for stratification factors age, sex, Ann Arbor stage, international prognostic score and hemoglobin level.

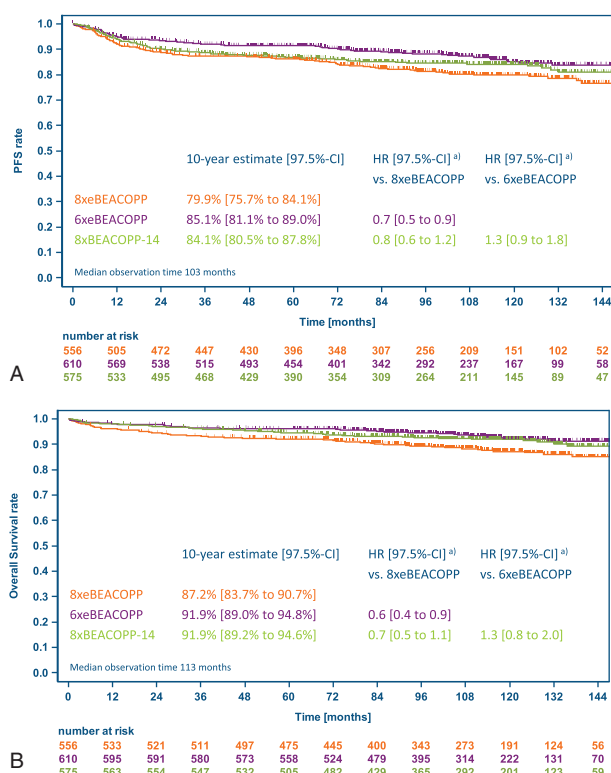


Figure 3. Kaplan-Meier estimates for the per-protocol set. (A) Progression-free survival. (B) Overall survival. BEACOPP-14=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in dose-dense variant, eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated dose, HR=hazard ratio, PFS=progression-free survival. (a) Hazard ratios adjusted for stratification factors age, sex, Ann Arbor stage, international prognostic score and hemoglobin level.

analysis comprising 1741 patients (Fig. 3A), 6xeBEACOPP proved to be significantly superior to 8xeBEACOPP, with a HR

of 0.7 (97.5% CI 0.5–0.9). PFS according to response to chemotherapy is displayed in Figure 4; 10-year estimates were 85% for those with complete remission, 88% for those with partial remission including residues of at least 2.5 cm in the largest diameter and a negative PET, and 85% for those receiving consolidating radiotherapy due to partial remission including residues of at least 2.5 cm in the largest diameter and a positive PET.

Among 209 patients with progression or relapse (Table 2), second PFS at 5 years was 54% (95% CI 47%–61%, Fig. 5), without differences between treatment groups (data not shown). With a median follow-up of 87 months after first progression or relapse, 84 (40%) of these patients died, including 51 deaths attributed to HL and 9 to toxicity of salvage therapy.

In total, 202 patients died within the follow-up period (Table 2). The SMR ranged from 4.5 (6xeBEACOPP) to 7.1 (8xeBEACOPP) and thus indicates an increased risk of death with respect to age- and sex-specific German reference data among all groups.⁷ When restricting the analysis to the long-term follow-up period starting 5 years after initial diagnosis, the most frequent cause of death was second malignancy (34 of 72 events), while at the time of the final analysis, most deaths had been attributed to HL. SMR_{long-term}, ranging from 3.2 to 4.0 (Table 2), was lower compared with the total study period, but still significantly elevated compared to the reference data.

Ten-year estimates for overall survival were 88% (97.5% CI 85%–91%), 90% (88%–93%), and 92% (89%–94%) with 8xeBEACOPP, 6xeBEACOPP and 8xBEACOPP-14, respectively, with a significant superiority of 6xeBEACOPP over 8xeBEACOPP (HR 0.7, 97.5% CI 0.5–0.999, $P=0.0245$) and a trend toward superiority of 8xBEACOPP-14 over 8xeBEACOPP (HR 0.7, 97.5% CI 0.5 to 1.04, $P=0.05$, Fig. 2B; per-protocol analysis: Fig. 3B).

A total of 142 patients were diagnosed with a second malignancy within the observed follow-up period (Table 2), including 40 patients with therapy-related acute myeloid leukemia or myelodysplastic syndrome (MDS), 3 with acute lymphoblastic leukemia (ALL), 29 with non-Hodgkin lymphoma

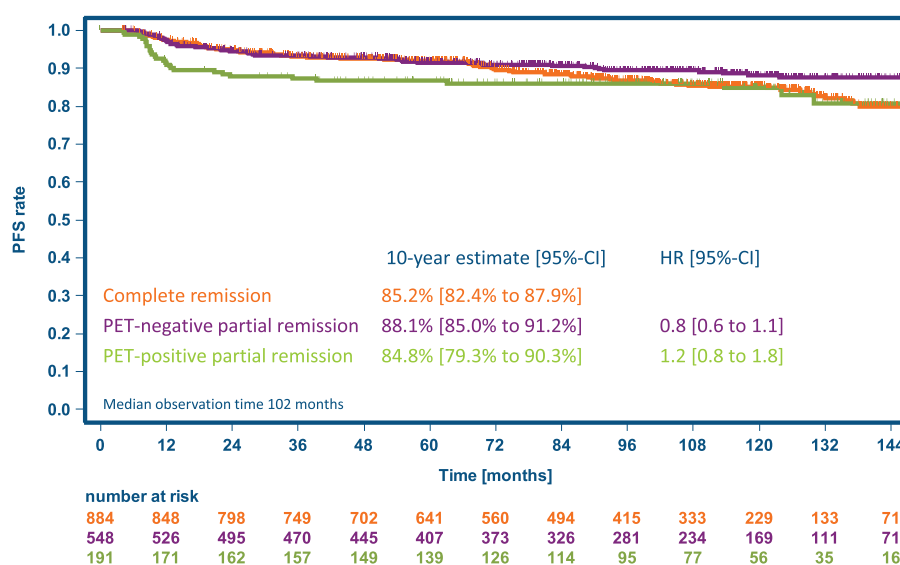


Figure 4. Progression-free survival by outcome after chemotherapy. Analysis includes patients with complete remission after chemotherapy and those with a partial remission, residual lesions of at least 2.5 cm in the largest diameter and centrally reviewed PET available. Radiotherapy was recommended in case of a positive PET scan. HR=hazard ratio, PFS=progression-free survival.

Table 2
Long-Term Outcomes of the Intention-to-Treat Set

	8xeBEACOPP (N = 705)	6xeBEACOPP (N = 711)	8xBEACOPP-14 (N = 710)	Total (N = 2126)
Observation time				
Observation time for disease status, median	104 months	102 months	101 months	102 months
Observation time for survival status, median	113 months	112 months	112 months	112 months
Tumor events				
Progression	25 (4%)	18 (3%)	20 (3%)	63 (3%)
Early relapse (within 1 year after end of treatment)	15 (2%)	16 (2%)	19 (3%)	50 (2%)
Late relapse	32 (5%)	24 (3%)	40 (6%)	96 (5%)
Any tumor event	72 (10%)	58 (8%)	79 (11%)	209 (10%)
Causes of death				
Second malignancy	24 (3%)	16 (2%)	19 (3%)	59 (3%)
HL	17 (2%)	16 (2%)	18 (3%)	51 (2%)
Toxicity of study treatment	15 (2%)	6 (1%)	7 (1%)	28 (1%)
Toxicity of salvage therapy	5 (1%)	2 (<1%)	2 (<1%)	9 (<1%)
Other disease*	10 (1%)	8 (1%)	4 (1%)	22 (1%)
Accident or suicide	1 (<1%)	3 (<1%)	2 (<1%)	6 (<1%)
Unclear	11 (2%)	8 (1%)	8 (1%)	27 (1%)
Any event	83 (12%)	59 (8%)	60 (8%)	202 (10%)
SMR (95% CI)	7.1 (5.6–8.7)	4.5 (3.4–5.8)	5.0 (3.8–6.5)	5.5 (4.8–6.3)
SMR _{long-term} (95% CI)	4.0 (2.6–5.9)	3.2 (2.0–4.7)	3.3 (2.1–5.0)	3.5 (2.7–4.4)
Second malignancies				
Leukemia or myelodysplastic syndrome	28 (4%)	3 (<1%)	12 (2%)	43 (2%)
Non-Hodgkin lymphoma	9 (1%)	13 (2%)	7 (1%)	29 (1%)
Solid tumor	22 (3%)	26 (4%)	23 (3%)	71 (3%)
Any malignancy	59 (8%)	42 (6%)	41 [†] (6%)	142 (7%)
SIR (95% CI)	4.3 (3.2–5.5)	2.5 (1.8–3.4)	2.8 (2.0–3.8)	3.2 (2.7–3.7)

Data are median or n (%) unless otherwise indicated. eBEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated dose.

BEACOPP-14 = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in dose-dense variant. SMR = Standardized mortality ratio. SIR = Standardized incidence ratio.

* Including cardiovascular disease (n = 5), pulmonary disease (n = 5), non-therapy-related infection (n = 4), liver disease (n = 1), brain disease (n = 1), alcohol abuse (n = 1) and unknown disease (n = 5).

[†] Including 1 patient diagnosed with secondary leukemia and solid tumor.

(NHL) and 71 with solid tumors (1 patient was diagnosed with secondary acute myeloid leukemia and then had a solid tumor). Of the 75 solid tumors diagnosed (4 patients had multiple tumors), most were in the lung (n = 20), digestive organs (n = 17), and skin (n = 14). Patients diagnosed with a second malignancy were significantly older compared with those without a second cancer diagnosis; the median age at study entry was 48 and 32 years, respectively ($P < 0.001$). The SIR ranged from 2.5 (6xeBEACOPP) to 4.3 (8xeBEACOPP) and was significantly elevated with respect to age- and sex-specific German reference data in all 3 groups (Table 2). In total, 59 of the 142 affected

patients (42%) died from their malignancy, with the highest proportion among those diagnosed with secondary leukemia or MDS (26 of 43 patients, 60%). Cumulative incidences of second malignancies after 10 years were 10% (97.5% CI 7%–13%), 7% (4%–9%), and 7% (4%–10%) with 8xeBEACOPP, 6xeBEACOPP and 8xBEACOPP-14, respectively, suggesting a possible trend toward higher incidence in the standard arm (Fig. 6A). Particularly, there were significantly more cases of secondary leukemia or MDS after treatment with 8xeBEACOPP, with 10-year cumulative incidences of 5% (97.5% CI 3%–7%), 1% (0%–1%), and 2% (1%–4%), respectively (Fig. 6B). There were also no differences between treatment arms regarding the occurrence of NHL or solid tumors (Table 2). There were also no differences regarding the occurrence of second malignancies between those 225 patients receiving consolidating radiotherapy and those 1901 patients who did not (Fig. 6C). Of the 3 solid tumors that occurred in patients who had received radiotherapy within our trial, only 1 was located within the radiotherapy field.

Discussion

The prospective randomized HD15 trial enrolled a total of 2182 patients with advanced-stage HL from 5 European countries and is the largest trial performed in this malignancy so far. With 10-year overall survival estimates of 88% and 90%, respectively, a significant benefit of 6xeBEACOPP over 8xeBEACOPP was detected. In addition, there were more cases of secondary leukemia/MDS with 10-year cumulative incidences of 5% with 8xeBEACOPP and 1% with 6xeBEACOPP, respectively; the proportion of patients diagnosed with solid tumors was 3%.

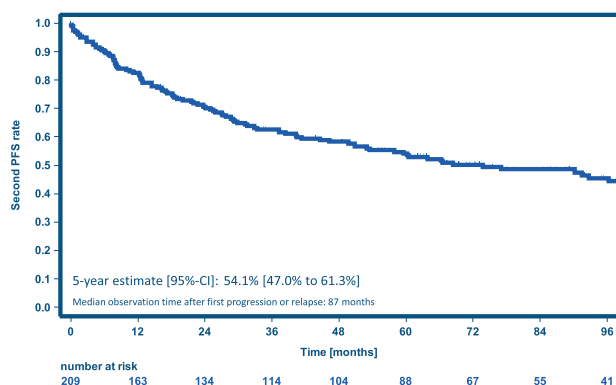


Figure 5. Second PFS for patients with progression or relapse. PFS = progression-free survival.

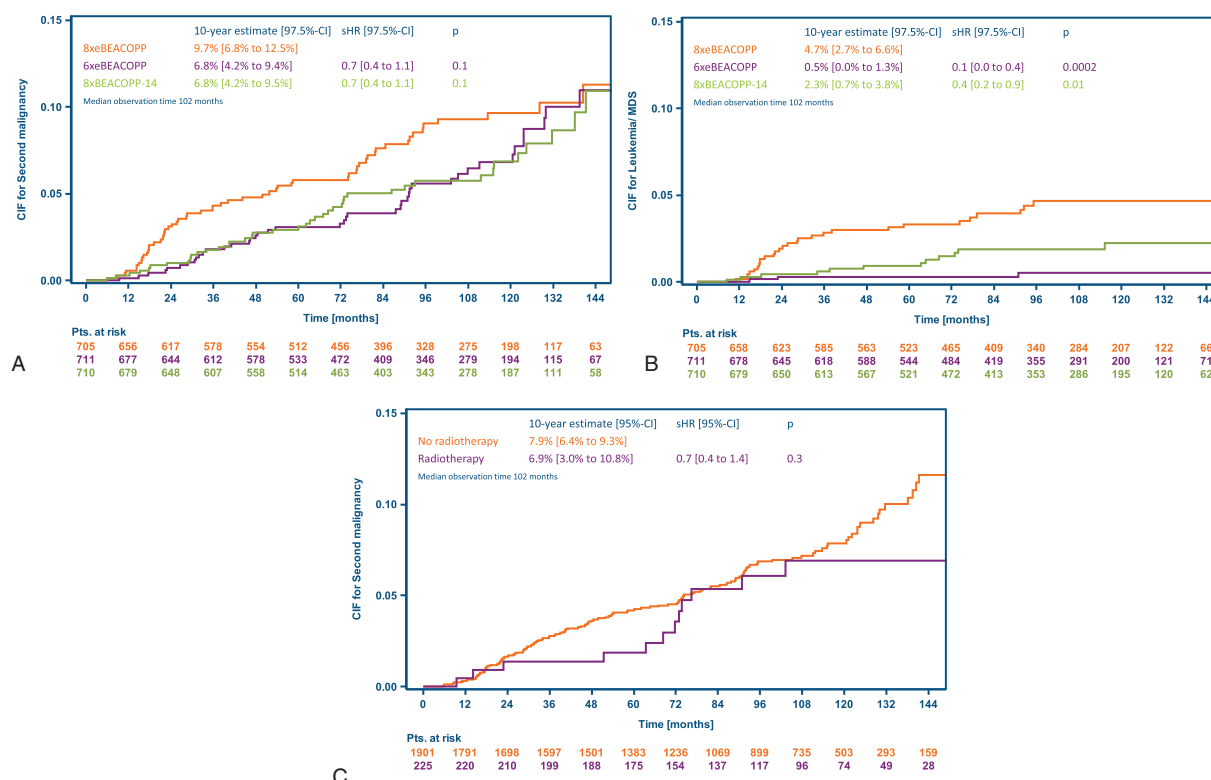


Figure 6. Cumulative incidence of second malignancies accounting for death as a competing risk. (A) Cumulative incidence of any second malignancy by treatment arm. (B) Cumulative incidence of secondary leukemia and myelodysplastic syndrome by treatment arm. (C) Cumulative incidence of any second malignancy by radiotherapy group (radiotherapy was recommended in case of partial remission including residual lesions of at least 2.5 cm in the largest diameter and a positive PET after chemotherapy). BEACOPP-14=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in dose-dense variant, CIF=cumulative incidence function, eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated dose, MDS=myelodysplastic syndrome, sHR=subdistribution hazard ratio.

The key objective in the treatment of HL, particularly regarding the first line of therapy, is to find the optimal balance between tumor control and treatment intensity. The HD15 trial can serve as an example, showing that 6 cycles of eBEACOPP are at least equally effective and at the same time less toxic as compared to the prior standard of 8 cycles.⁵ Following HD15, 6 cycles of eBEACOPP became the new standard in advanced-stage HL. In addition, radiation could be confined to PET-positive residues measuring 2.5 cm or more. The favorable long-term PFS of patients with a PET-negative partial remission after chemotherapy demonstrated in the current update supports this PET-guided radiation strategy.

More recently, PET in advanced-stage HL has been used to discriminate low-risk from high-risk patients.⁸ The UK RATHL trial showed that after 2 cycles of ABVD, PET-negative HL patients can be safely spared from additional bleomycin.⁹ The GHSG was also able to further reduce the intensity of treatment in advanced-stage HL: The randomized phase 3 HD18 trial demonstrated that patients with a negative PET after 2 cycles of eBEACOPP need only 2 more cycles, rendering 4 cycles of eBEACOPP the new standard of care in early-responding patients.¹⁰ Thus, treatment with 6xeBEACOPP as established in the HD15 trial are still considered standard of care in patients with advanced-stage HL and a positive PET after 2 cycles of eBEACOPP.¹¹

With an intensified front-line treatment particularly in advanced-stage patients, the number of relapses has been

substantially reduced over time.^{4,5,10,11} Long-term follow-up reports in HL are rare but particularly relevant in order to better understand risk factors for late relapses and how to better avoid long-term toxicity in this group of young cancer patients. As far as long-term results are concerned, only smaller case series with rather few patients who relapsed after 5 years in remission have been reported to date.^{12–14} The GHSG retrospectively analyzed patients included in the HD7 to HD12 trials with a median observation period of 10 years.^{15,16} Patients who experienced a relapse after more than 5 years in remission were compared with those in continued remission for more than 5 years. From a total of 4953 patients who had achieved CR after first-line treatment and were relapse-free for at least 5 years, 141 patients with late-relapsed HL were identified. Interestingly, the cumulative incidence of late HL relapses rose in a linear fashion with no plateau observed and an estimate of 6.9% late relapses at 20 years after initial diagnosis. More importantly, the risk for developing HL after being free for at least 5 years was about 85-fold increased as compared to an age- and sex-matched general population. On the other hand, more than half of the patients could still be salvaged even if they had received an intensive combination as initial therapy.

Despite the fact that the majority of HL patients achieve lasting complete remission upon first-line treatment, there still is a considerable risk of late events such as second malignancies,^{17–20} organ damage to lung,²¹ heart,²² as well as infertility²³ and fatigue.^{24,25} In this update analysis of HD15, there were

significantly more cases of secondary leukemia/MDS after treatment with 8xBEACOPP, with 10-year cumulative incidences of 5% as compared to 1% with 6xBEACOPP and 2% with 8xBEACOPP-14, respectively. Most secondary leukemia/MDS occurred in the 5-year observation period ($n=29$)²⁶ as compared to 14 new cases in years 5 to 10, respectively. In contrast, the number of patients diagnosed with solid tumor rose from a total of 24 (1.2%) at 5 years of follow-up to 71 (3%) at the present 10-year analysis, implying the particular relevance of keeping track of the development of second cancer even beyond this 10-year follow-up report.

As shown in this update of the HD15 trial, HL patients are at increased risk of death compared with an age- and sex-matched general population: the reported SMRs were 7.1 for 8 cycles of eBEACOPP and 4.5 for 6 cycles of eBEACOPP, respectively. With longer follow-up, death from HL has become less common; on the other hand, other causes of death such as second cancers were diagnosed more frequently. Importantly, when the mortality analysis was restricted to the long-term follow-up period, SMRs still implied a significantly elevated risk of death also in patients who survived the first 5 years after their HL diagnosis. Thus, there is clearly a need for more specific new drugs particularly for this young patient population. In addition, the response rates to checkpoint inhibitors such as nivolumab or pembrolizumab in very heavily pretreated HL patients indicate that the Hodgkin and Reed-Sternberg cells are highly susceptible to the blockade of the PD1-PD ligand axis.^{27,28} These agents might therefore be used to further decrease the intensity of conventional chemo- and or radiotherapy in HL.

The major limitation of the current analysis is the uncertainty related to the number of events to be observed with even longer follow-up. Here, in particular the number of second cancers and their outcomes will be extremely relevant. In addition, we have no comprehensive long-term data on cardiovascular complications such as heart failure. The major strength of this analysis is the large data set and the extended observation period allowing reasonable conclusions. In particular, we gained updated information from nearly 90% of our patients.

The current follow-up analysis of the GHSG HD15 trial clearly underscores the relevance of comprehensive long-term outcome analyses in HL patients and adds relevant data on both, tumor control and safety.

Acknowledgments

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4. Postavení brentuximab vedotinu v léčbě relapsu Hodgkinova lymfomu

Léčebný management relabujícího nebo primárně refrakterního klasického Hodgkinova lymfomu (rr-cHL) prošel v uplynulé dekádě pozoruhodným vývojem, v němž brentuximab vedotin (BV) představuje jeden z významných pilířů záchranné léčby. BV je konjugát monoklonální protilátky cílené proti antigenu CD30 s cytotoxickou látkou monomethyl auristatin E (MMAE). Po vazbě BV na CD30 dochází k internalizaci komplexu a jeho transportu do lysozomů, kde je proteolyticky štěpen linker spojující protilátku s cytotoxickou složkou. Následně uvolněný monomethyl auristatin E (MMAE) inhibuje polymerizaci mikrotubulů, což vede k zástavě buněčného cyklu a apoptóze nádorových buněk. Tento mechanismus umožňuje cílené působení cytotoxické látky na CD30 exprimující nádorové buňky. K protinádorovému účinku BV může přispívat také tzv. bystander efekt, při němž MMAE uvolněný z cílových buněk působí i na okolní nádorové buňky s nízkou nebo chybějící expresí CD30.^{52,53}

Význam BV byl nejprve prokázán u pacientů s relabovaným nebo refrakterním HL po autologní transplantaci krvetvorných buněk. Pivotní studie fáze II zahrnující 102 pacientů prokázala celkovou míru léčebné odpovědi (ORR) 75 %, přičemž kompletní remise (CR) bylo dosaženo u 34 % nemocných. Medián přežití bez progresu u všech pacientů činil 5,6 měsíce a medián trvání odpovědi u nemocných, kteří dosáhli kompletní remise, činil 20,5 měsíce.⁵² Dlouhodobé pětileté sledování této kohorty potvrdilo trvalost léčebného účinku u části pacientů; pětileté celkové přežití celé studované populace činilo 41 % a pětileté přežití bez progresu 22 %.⁵⁴

Významným posunem v léčbě pacientů po autologní transplantaci byla studie AETHERA, která hodnotila jednoroční konsolidační léčbu BV u nemocných s vysokým rizikem relapsu nebo progresu po autologní transplantaci krvetvorných kmenových buněk (autologous stem cell transplantation, ASCT). Mezi hlavní rizikové faktory patřil primární refrakterní HL, relaps HL do 12 měsíců od ukončení primární léčby a relaps s extranodálním postižením. Pětileté přežití bez progresu dosáhlo 59 % u pacientů léčených BV ve srovnání se 41 % u pacientů užívajících placebo.^{55,56} Tyto výsledky vedly k zařazení BV mezi možnosti konsolidační léčby pacientů s vysokým rizikem relapsu po ASCT.

Dalším významným směrem vývoje je využití BV již v rámci záchranné léčby před ASCT. Cílem záchranné terapie je dosažení co nejhlubší metabolické odpovědi před vysokodávkovanou chemoterapií a následnou autologní transplantací. BV byl proto zkoumán jak v monoterapii, tak v kombinaci s chemoterapií nebo dalšími novými léčivy. Kombinace BV s bendamustinem prokázala vysokou účinnost jako úvodní záchranná léčba a umožnila následné provedení ASCT u významné části pacientů.⁵⁷

Pozornost byla věnována rovněž kombinaci BV s inhibítozem PD-1 nivolumabem. Ve studii fáze I/II byla tato kombinace použita jako úvodní záchranná léčba u pacientů s relabovaným nebo refrakterním cHL. Celková míra léčebné odpovědi činila 82 % a kompletní remise bylo dosaženo u 61 % pacientů. Kombinace byla obecně dobře tolerována a umožnila následné provedení ASCT u značné části nemocných.⁵⁸ Dlouhodobější výsledky této strategie následně potvrdily její vysokou účinnost a podporují její využití jako jedné z možností záchranné léčby u vhodně vybraných pacientů.⁵⁹

Za hlavní cíl následující publikace lze považovat zhodnocení účinnosti BV u pacientů s relabovaným nebo refrakterním HL v podmínkách běžné klinické praxe v České republice a na Slovensku. Studie ukázala, že léčebné výsledky dosažené mimo prostředí klinických studií jsou srovnatelné s výsledky klíčových registračních studií a dalších analýz reálné klinické praxe, což podporuje přenositelnost výsledků BV do rutinní klinické péče. Dalším významným přínosem bylo hodnocení homogenního souboru pacientů léčených ve specializovaných hematologických centrech ve dvou zemích se srovnatelnou organizací zdravotní péče. Vyšší četnost kompletních remisí u pacientů s menším počtem předchozích léčebných linií naznačuje, že časnější zařazení BV do léčebného algoritmu může být spojeno s vyšší účinností léčby. Tyto výsledky rozšiřují poznatky o využití BV u relabovaného nebo refrakterního HL v podmínkách běžné klinické praxe a poskytují další podklady pro individualizaci léčebné strategie.

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Research Paper

Treatment of Relapsed/Refractory Hodgkin Lymphoma: Real-World Data from the Czech Republic and Slovakia

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Abstract

Introduction: Clinical trials have demonstrated the effectiveness of the CD30-targeted antibody–drug conjugate brentuximab vedotin (BV) for the treatment of relapsed/refractory Hodgkin lymphoma (R/R HL). In this study, we report on outcomes with BV in a real-world setting using data collected in clinics in the Czech Republic and Slovakia.

Patients and Methods: Clinical and epidemiological data for patients with R/R HL who received treatment with BV at eight centers across the Czech Republic and Slovakia were examined. Data were amalgamated and analyzed retrospectively.

Results: Clinical data for 58 patients (median age: 30.5 years) with R/R HL who received BV during the course of their treatment were collected and analyzed. Patients had received a median of 3 prior treatment regimens and most (91%) were treated with BV after relapse following autologous stem cell transplantation. Therapeutic responses after BV included 19 (33%) complete responses (CRs) and 8 (14%) partial responses. CRs occurred more frequently in patients who had received fewer prior treatment regimens. The 1-, 2-, and 3-year overall survival (OS) rates from initiation of BV were 78%, 62%, and 41%, respectively.

Conclusion: Response rates and OS in this analysis of BV in real-world settings in the Czech Republic and Slovakia were consistent with those reported for pivotal clinical trials and from previous studies outside the clinical trial setting. The results support the efficacy of BV for treatment of R/R HL in real-life clinical practice.

Key words: antibody–drug conjugate; CD30; brentuximab vedotin; Hodgkin lymphoma; registries; stem cell transplantation

Introduction

Treatment for Hodgkin lymphoma (HL) achieves very high cure rates, with most patients (>80%) achieving a cure and long-term survival.

However, approximately 20–40% of patients experience a relapse after front-line therapy or fail to respond to initial treatment, with approximately 50%

of these patients being subsequently salvaged by high-dose chemotherapy followed by autologous stem cell transplantation (ASCT), which is the standard of care for most patients according to the European Society for Medical Oncology (ESMO) guidelines for the management of HL.¹⁻⁵ In patients with failure after ASCT the outlook is poor, with a median survival of only 25 months.⁶

A number of factors that are predictive of outcome after ASCT have been identified, such as early (<12 months) relapse after ASCT, disease refractory to front-line therapy, failure to achieve a response to the most recent salvage therapy, extranodal disease (stage IV) or B-symptoms at pre-ASCT relapse, prior use of two or more salvage therapies, bulky disease, poor performance status, and age ≥ 50 years at relapse. Patients with one or more of these factors have worse outcomes after ASCT.⁷ Furthermore, some patients are not eligible for ASCT due to factors such as age, refractory disease, or poor performance status. For these patients, new treatment strategies are needed urgently.

Brentuximab vedotin (BV) is a CD30-targeting antibody–drug conjugate that was shown in a pivotal phase II trial to be an effective and well-tolerated treatment for patients with relapsed/refractory (R/R) HL after ASCT with an overall objective response rate (ORR) of 75% and complete remission in 34% of patients.⁸ Recently published 5-year follow-up data from the trial showed that durable responses could be achieved even without further anticancer therapy, with 9 of the 34 patients (26%) who achieved a complete response (CR) still in remission and potentially cured.⁹ Studies have also shown that BV is an effective option for patients with R/R HL who are ineligible for transplantation.^{10,11}

While clinical trials are critical for establishing efficacy, collection of real-world data outside of the controlled trial setting is important to evaluate how interventions are applied and assess the effectiveness of new treatments in routine clinical practice. Inclusion criteria are often rather restrictive compared with the patient populations seen by physicians in daily practice.

There are limited real-world data related to treatment with BV, and where it is available, efficacy and safety are consistent with those seen in clinical trials. Five retrospective observational studies have collected data for more than 200 patients with R/R HL treated with BV in centers in Asia, France, Italy, and Turkey.¹²⁻¹⁶ Across the studies, ORRs were in the range of 40–73%, and CRs were reported for 18–34% of patients. For the four studies that reported median progression-free survival (PFS), these ranged from 6.6 to 9.0 months. The most frequently observed adverse

events across the studies included sensory neuropathy and neutropenia.

The present study investigates a population of patients who have received a median of 3 previous treatment regimens. These patients represent those who have relapsed and may then have a critical medical need, requiring a different management strategy to standard salvage therapy. We report the results of a retrospective, observational study with the objective of assessing the effectiveness and tolerability of BV for the treatment of R/R HL in a real-world setting, based on complementary data collected in a collaboration between institutes in the Czech Republic and Slovakia.

Methods

This retrospective, observational study examined data for patients with R/R HL at eight centers in the Czech Republic and Slovakia. In the Czech Republic, data came from a clinical registry of patients with R/R HL who started treatment with BV between May 2013 and November 2015. An identical data collection strategy was used in Slovakia for patients who started BV treatment between July 2012 and January 2016. All patients were treated within government-funded schemes, with no patients included from clinical trials or named patient programs. Patients were CD30-positive, as determined by immunohistochemical examination on entry biopsy, typically with positivity in the membrane and Golgi apparatus in Hodgkin's and Reed-Sternberg cells of classical HL.

The analysis included data for patients who received BV for the treatment of R/R HL following ASCT or who were ineligible for ASCT after failure of one previous salvage therapy. BV was initiated at the recommended dosing of 1.8 mg/kg every 3 weeks for up to a maximum of 16 cycles.

The data collected and examined included patient characteristics and demographics, prior treatment history, details of BV treatment, clinical responses to BV treatment, and survival outcomes. Clinical responses were evaluated according to the revised Cheson criteria (2007),¹⁷ with all patients assessed by computed tomography before initiating BV and after 4, 8, 12, and 16 cycles of treatment as applicable. Use of positron emission tomography (PET) was not reimbursed within the government-funded schemes and was not routinely available. Overall survival (OS) was determined both from the time of HL diagnosis and the initiation of BV treatment.

Primary data were expressed using absolute and relative frequencies for categorical variables, and median and range (5–95 percentiles) for continuous

variables. Differences between patient groups were assessed using the non-parametric Fisher exact test, Mann-Whitney U test, or Kruskal-Wallis test.

The analyses employed logistic regression models to quantify the association between potential predictors and principal, binary-coded endpoints (i.e. relapse rate, response to the therapy) using both univariate and multivariate-adjusted approaches. The models used maximum likelihood estimation, directly comparing the likelihood L0 for the null model where all slope parameters are zero, with the likelihood L1 of the fitted model. Significance of regression coefficients was tested using the Wald test statistic, which is based on the asymptotic normality property of maximum likelihood estimates (tested on the basis of Chi-square distribution). Similarly, univariate and multivariate Cox proportional hazard regression models were applied to test the impact of potential predictors on OS as a time-to-event endpoint. Both univariate and multivariate-adjusted estimates of odds ratio (OR) and hazard ratio (HR) were determined with 95% confidence intervals. Standard Kaplan-Meier curves were used to display OS profiles stratified according to clinical stage. Log-rank testing was used to assess the statistical significance of differences across the strata.

The study was conducted according to the principles expressed in the Declaration of Helsinki. Informed consent from the participants was not collected as all data were analyzed anonymously.

Results

Patient characteristics and treatment history

A total of 58 patients with R/R HL who had received treatment with BV were identified in the institutional databases and included in the retrospective analysis. Patient and disease characteristics, as well as the treatment history for the 58 patients, are summarized in **Table 1**. The median age of patients at diagnosis was 30.5 years, and the median follow-up from diagnosis was 4.3 years from diagnosis and 1.4 years from BV initiation.

Patients had received a median of 3 treatment regimens prior to treatment with BV. The majority of patients (86%) had previously received doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) at some point in the course of their treatment. Other frequently used chemotherapy regimens included bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisolone (BEACOPP), dexamethasone/high-dose cytarabine/cisplatin (DHAP) and ifosfamide/carboplatin/etoposide (ICE). The proportion of patients who had received radiotherapy was 69%.

Most patients (91%) had received at least one ASCT and 12% had had an allogeneic stem cell transplant (allo-SCT). Of the patients receiving prior ASCT, 7 patients underwent 2 transplants prior to BV administration, three of which were tandem-ASCTs with an inter-transplant interval of 5–7 months. Based on the activity of the disease, patients in this study were divided into two groups prior to initiating BV – 52 patients (90%) were in relapse with progressive disease (PD) and 6 patients (10%) had partial stabilization (i.e. they had either partial response [PR] or stable disease [SD]). Patients with PR/SD receiving BV treatment were those whose prior therapy did not lead to CR, despite 5 of these 6 patients having undergone ASCT, two of which were tandem-ASCTs.

Table 1: Patient characteristics and treatment history

		N (%)	Median (5–95 percentiles)
Patient characteristics			
Length of follow-up (years)		4.3	(1.2–16.0)
Age at time of diagnosis		30.5	(20.0–53.0)
Sex	Men	33	(57)
	Women	25	(43)
HL stage	I+II	23	(40)
	III	19	(33)
	IV	16	(28)
Indication for BV	Relapse after autologous transplantation	53	(91)
	R/R, unsuitable for ASCT	5	(9)
Pretreatment			
Number of regimens		3.0	(2.0–9.0)
Previous regimens ^a	ABVD	50	(86)
	BEACOPP	21	(36)
	COPP	15	(26)
	DHAP	26	(45)
	Gemcitabine	9	(16)
	ICE	26	(45)
	IGEV	9	(16)
	Other	29	(50)
	Radiotherapy	18	(31)
	Yes	40	(69)
ASCT	No	5	(9)
	Yes – 1 transplant	46	(79)
	Yes – 2 transplants	7	(12)
Allo-SCT	No	51	(88)
	Yes	7	(12)
Response before BV	PD/relapse	52	(90)
	PR/SD	6	(10)

^aTreated with regimen at any stage in treatment history; only regimens assigned to at least five patients are listed. ABVD: doxorubicin, bleomycin, vinblastine and dacarbazine; allo-SCT: allogeneic stem cell transplantation; ASCT: autologous stem cell transplantation; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone; BV: brentuximab vedotin; COPP: cyclophosphamide, vincristine, procarbazine and prednisolone; DHAP: dexamethasone, high-dose cytarabine and cisplatin; HL: Hodgkin lymphoma; ICE: ifosfamide, carboplatin and etoposide; IGEV: ifosfamide, gemcitabine and vinorelbine; PD: progressive disease; PR: partial response; R/R: relapsed/refractory; SD, stable disease.

Safety

All patients received at least 3 doses of BV with a median 7.5 cycles (range, 3–16 cycles). Only 1 patient (2%) required a reduction in the dose of BV to 1.2

mg/kg due to neutropenia (Grade 3/4), while dosing delays were instituted for 8 (14%) of the patients. Toxic effects of BV which lead to a prolongation of the dose interval included 2 cases of leukopenia (Grade 3/4), 1 case of urinary tract infection, 2 cases of acute bronchitis, 1 case of odontogenic infection and 1 case of increase in pancreatic amylase. In our retrospective study, the most common toxic manifestation of BV was neurological toxicity, which was observed in 21 patients (36.2%). Of these, 12 patients presented with peripheral sensory neuropathy (Grade 1/2) only, 3 patients with peripheral motor neuropathy (Grade 1/2) only, and 6 patients with simultaneous occurrence of sensory and motor neuropathy (Grade 1/2).

Therapeutic responses to brentuximab vedotin

Patients received a median of 7.5 cycles of BV treatment. Of the 58 patients, 19 (33%) had a CR following BV treatment, with 8 (14%) having a PR and 31 (53%) having PD (Table 2). Discontinuation of BV was due to disease progression, negotiations with health insurance companies, or receipt of allo-SCT. Following treatment failure with BV, 6 patients received nivolumab, with 3 patients subsequently achieving CR. Of the remaining 3 patients, 2 progressed and 1 died of septic shock while on nivolumab therapy.

Table 2: Treatment and outcomes after brentuximab vedotin treatment

		N (%)	Median (5–95 percentiles)
BV treatment			
Number of BV cycles		7.5	(3.0–16.0)
Number of BV cycles	2–5	20	(35)
	6–10	29	(50)
	11–16	9	(16)
Dose reduction	No	57	(98)
	Yes	1	(2)
Interval change ^a	No	16	(67)
	Yes	8	(33)
Response during treatment	CR	8	(14)
	PR	26	(45)
	SD	7	(12)
	PD	12	(21)
	Not available	5	(9)
Outcome			
Response on BV	CR	19	(33)
	PR	8	(14)
	PD	31	(53)
Relapse ^b	No	21	(78)
	Yes	6	(22)
Death	No	38	(66)
	Yes	20	(35)

Data are presented as N (%) or median (5–95 percentiles). ^aData are not available for 34 patients. ^bRelapse occurrence was assessed only in patients with a CR or PR on BV treatment.

BV: brentuximab vedotin; CR: complete response; PD: progressive disease; PR: partial response; SD: stable disease.

Of the 58 patients treated with BV, the duration of the therapeutic response was evaluated in 34

patients, with the median being 5 months. Of the remaining patients, 13 patients achieving a response to BV were directed to allo-SCT, and the remaining 11 patients are alive with no signs of relapse/progression of HL.

Patients who achieved a CR after BV subsequently received more cycles of treatment (median 8 cycles) as they did not relapse during BV treatment. Patients with an inadequate response to BV received fewer cycles (PR, median 5.5 cycles; PD, median 6 cycles) mostly due to the poor response ($P < 0.001$). BV treatment was discontinued early (patients received < 8 cycles of BV) in a total of 29 patients. Of these, 19 patients discontinued treatment due to insufficient response to BV. Six patients discontinued BV treatment early due to redirection to allo-SCT, of which 3 patients were in PR following 3, 5 and 6 cycles of BV, and 3 patients were in CR following 6, 3 and 6 cycles. The number of BV cycles was also influenced by negotiations with health insurance companies, which lead to the decision to discontinue BV treatment early in 2 patients who achieved CR. No patients discontinued treatment early due to toxicity or drug availability issues, and the remaining 2 patients discontinued treatment early due to unknown reasons.

Patients receiving fewer previous treatment regimens were more likely to achieve a CR. Univariate and multivariate logistic regression models confirmed these associations, and that none of the other factors tested were significantly correlated with the likelihood of achieving a CR (data in Supplementary Table S1).

No factor was found to be significantly associated with the risk of relapse in univariate or multivariate logistic regression models (Supplementary Table S2). Overall, 14 patients underwent allo-SCT after BV treatment. CR was achieved following allo-SCT in all patients who received the transplant in CR (6 patients) or PR (3 patients). Of the remaining 5 patients receiving allo-SCT with PD, CR was achieved in 2 cases.

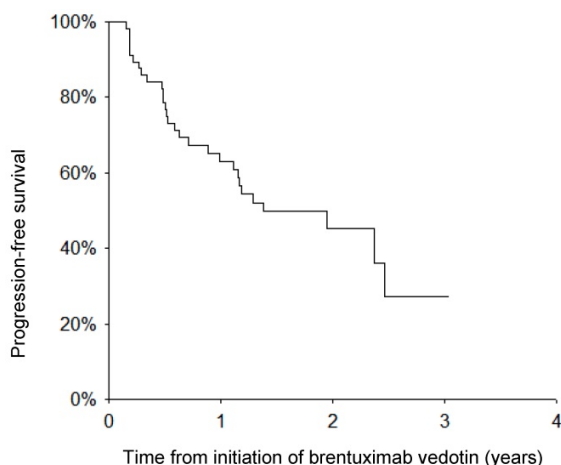
Progression-free survival

Figure 1 shows the PFS for the 58 patients from the start of BV therapy. The PFS rates at 1 and 2 years were 63.2% and 45.2%, respectively. The median PFS was 1.38 (0.56–2.21) years.

Overall survival

At 1 and 3 years after initiation of BV, OS was 78% and 41%, respectively (Figure 2A). The OS rate at 1 year after BV initiation was 96% for patients with Stage I or II disease at diagnosis, compared with 78% for Stage III disease and 56% for Stage IV disease (Figure 2B). In a univariate analysis, OS from

initiation of BV was significantly shorter in patients initially diagnosed with more advanced stage HL, and significantly longer in patients who received six or more cycles of BV compared with those who received five or fewer cycles ($P < 0.05$; **Supplementary Table S3**).



	PFS (95% CI)
1-year	63.2% (50.2%; 76.1%)
2-year	45.2% (29.9%; 60.5%)

CI, confidence interval; PFS, progression-free survival.

Figure 1: Progression-free survival of patients with Hodgkin lymphoma from initiation of brentuximab vedotin

Discussion

Our study reports and assesses data related to the treatment of R/R HL, and specifically BV, in clinical practice in a 'real-world' setting. This information can provide a valuable complement to findings from randomized clinical trials, capturing experience in routine clinical practice rather than the selected, highly controlled trial conditions.

The characteristics of the patients included in our study were typical of those encountered in real-life practice who are eligible for treatment with BV. Comparing our observational study with the pivotal phase II clinical trial of BV in R/R HL, the median age of patients (30.5 and 31 years, respectively) was the same, and the median number of prior chemotherapy regimens (3.0 and 3.5, respectively), proportion of patients who had previously received at least one ASCT (both 91%) and the proportion who had received radiotherapy (69% and 67%, respectively) were all similar.⁸ Some differences exist between the study populations: in the pivotal phase II trial, for example, all patients had undergone ASCT, whereas the present study included

5 patients who were ineligible for ASCT. Response assessment also differed: while the phase II trial included both computed tomography and PET scans in the trial design, the present study evaluated response by computed tomography only – PET scans were not routinely available in this retrospective analysis. While results may have been different with a PET-driven approach, this study was not a clinical trial, and PET/CT is not always a standard procedure for interim disease response evaluation in routine clinical practice, even in countries other than the Czech Republic and Slovakia.

Most patients (86%) had received an ABVD regimen, and a substantial proportion had received BEACOPP (36%), as part of their treatment history prior to BV, reflecting that some patients were switched from BEACOPP to ABVD due to toxicity issues. This suggests that practice in the centers in the Czech Republic and Slovakia is consistent with ESMO guidelines, which recommend either ABVD or BEACOPP as front-line treatment for newly diagnosed HL.³ Frequently used salvage regimens included DHAP and ICE. The high proportion of patients who had previously received at least one ASCT (91%), with the exceptions being those unsuitable for ASCT, reflects that use of BV followed the licensed indications for BV as well as ESMO recommendations.^{3,18}

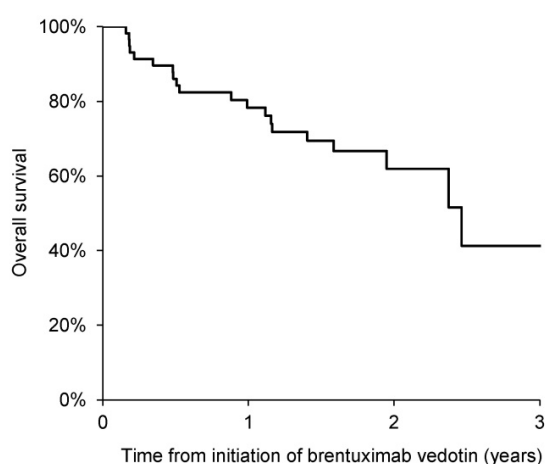
Seven patients (12%) had received prior allo-SCT, consistent with ESMO guidelines that this is not a standard approach in HL but can be considered for young patients in good general condition with relapse after ASCT.³ Of these 7 patients, 4 achieved CR following subsequent treatment with BV, none of whom relapsed. BV treatment in patients post-allo-SCT has thus far not been studied extensively. A previous study of 25 patients with HL relapsing after allo-SCT, indicated that BV treatment had potential utility in post-allo-SCT management, resulting in a 38% CR rate.²⁰ Although a small number, the results of the present study provide further support for the efficacy of BV treatment post-allo-SCT.

The response rates after treatment with BV are mostly consistent with previous studies. For example, the CR rate of 33% following BV treatment among patients in our clinics in the Czech Republic and Slovakia was the same as that seen in a long-term follow-up of patients in the pivotal phase II trial.⁹ The ORR (47%) and CR rates in our study were also within the range reported from other observational studies (ORR: 40–73%; CR: 18–34%).^{12–16} Based on the analysis of experience in our clinics, patients who received less extensive prior treatment were more likely to achieve CR, and subsequently a higher number of cycles of BV

treatment. There was some indication that the risk of relapse was increased when the dosing interval of BV was changed from that recommended, but the small number of patients for whom relevant data were available limits interpretation. In patients with PD after BV, there was a longer interval between BV cycles. The cause of prolongation between BV cycles was most often due to infectious complications (respiratory tract infections) and myelotoxicity. It is not currently clear how to distinguish between those patients who are likely to gain the greatest benefit from BV treatment (i.e. long-term remission) and therefore do not require any further consolidation and those for whom BV therapy should serve as a bridge to allo-SCT. A recent review of published reports from the named patient program for BV, drawing together experience from 480 patients with R/R HL in

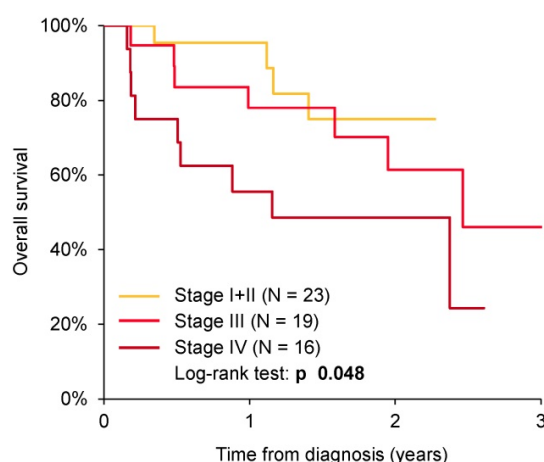
approximately 60 countries, found 1-year OS rates of 67–76% and 2-year OS rates of 58–67% from the initiation of BV treatment.²¹ Survival rates in our study were consistent with the results from the named patient program, with 1- and 2-year OS rates of 78% and 62%, respectively. Comparing these results in real-world settings with those from clinical trials, in the pivotal phase II trial with BV, the estimated 1-year OS rate was somewhat higher at 89% and in long-term follow-up the 5-year OS rate was 41%.^{8,9} The duration of therapeutic response (5 months) appears to be lower than that observed in previous pivotal and real-world studies.^{8,12,13,15,21} This may be due to the inclusion of more heavily pretreated patients with R/R HL, who had previously undergone 2–9 previous chemotherapy regimens, as well as prior ASCT and allo-SCT.

(A)



	OS (95% CI)
1-year	78.3% (67.4%; 89.2%)
2-year	61.9% (46.6%; 77.2%)
3-year	41.3% (15.8%; 66.8%)

(B)



OS (95% CI)	Stage I+II	Stage III	Stage IV
1-year	95.5% (86.8%; 100.0%)	78.0% (59.0%; 97.1%)	55.6% (30.9%; 80.2%)
2-year	75.0% (53.4%; 96.6%)	61.4% (36.0%; 86.8%)	48.6% (23.5%; 73.7%)
3-year	-	46.1% (13.8%; 78.4%)	-

CI, confidence interval; OS, overall survival.

Figure 2: (A) Overall survival of patients with Hodgkin lymphoma from initiation of brentuximab vedotin and (B) according to disease stage

By drawing on real-world data, our study provides further evidence on the use and effectiveness of BV in routine clinical practice. The use of BV in R/R HL management should be considered in the context of other treatment options, such as immune checkpoint inhibitors.²²⁻²⁵ Data were collected using a consistent, standardized and systematic approach that allowed a robust analysis. At the same time, common to other real-world analyses, our study is potentially open to numerous confounding factors and sources of bias that would, to some extent, be reduced by the restrictions and controls of a prospective clinical trial. The number of patients included in the analysis was also relatively small, reducing the scope for sub-analyses and interpretation, which means that valid conclusions can only be drawn from a limited number of statistical tests. In conclusion, this analysis of real-world data for patients with R/R HL in the Czech Republic and Slovakia, demonstrated efficacy with BV consistent with that seen in previous reports from real-world practice as well as clinical trials.

Supplementary Material

Supplementary tables.

<http://www.jcancer.org/v10p5041s1.pdf>

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Competing Interests

Zdeněk Král, MD, consultancy/advisory board member: Takeda, speaker for: Amgen, Teva, research support from: no, stock options with: no, consultancy for: Takeda.

Jozef Michalka, MD, consultancy/advisory board member: no, speaker for: no, research support from: no, stock options with: no, consultancy for: no.

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5. Význam PET u relabujícího Hodgkinova lymfomu

Přestože většina nemocných s HL dosahuje po primární léčbě dlouhodobé remise, přibližně u 10–20 % pacientů dochází k relapsu onemocnění nebo je onemocnění refrakterní vůči úvodní léčbě. U pacientů způsobilých k intenzivní léčbě představuje standardní kurativní postup u relabovaného nebo refrakterního onemocnění záchranná systémová léčba následovaná vysokodávkovanou chemoterapií a ASCT. V tomto diagnosticko-terapeutickém algoritmu představuje PET/CT klíčovou zobrazovací metodu pro stanovení rozsahu onemocnění, hodnocení léčebné odpovědi a prognostickou stratifikaci pacientů. Při podezření na relaps má PET/CT zásadní význam pro posouzení rozsahu suspektního postižení a pro výběr optimálního místa k odběru reprezentativního vzorku tkáně k následnému histologickému vyšetření. Ve srovnání se samotným CT umožňuje přesněji posoudit přítomnost metabolicky aktivního reziduálního onemocnění a odlišit je od reziduálních vazivových či fibrotických změn přetrvávajících po předchozí léčbě, zejména v mediastinální oblasti.^{53,60,61}

Vyšetření PET/CT navíc umožňuje stanovit před zahájením záchranné léčby výchozí metabolický nádorový objem (baseline metabolic tumor volume, bMTV). Moskowitz et al. prokázali, že vyšší bMTV je u pacientů s relabujícím nebo refrakterním cHL spojeno s kratším přežitím bez příhody (event-free survival, EFS) a představuje nezávislý prognostický faktor.²⁹

Zásadní prognostický význam má hodnocení metabolické odpovědi pomocí PET/CT před provedením ASCT. Dosažení kompletní metabolické odpovědi, zpravidla definované jako Deauville skóre 1–3, patří mezi nejvýznamnější prognostické ukazatele výsledku po záchranné léčbě a ASCT. Pacienti s negativním PET/CT nálezem před ASCT dosahují významně lepšího přežití bez progresu nebo příhody než nemocní s přetrvávajícím metabolicky aktivním onemocněním.^{61,62}

Tyto poznatky vedly k rozvoji PET-adaptovaných léčebných strategií u relabovaného nebo refrakterního HL. Cílem moderní záchranné léčby je dosáhnout co nejlepší, ideálně kompletní metabolické odpovědi ještě před vysokodávkovanou přípravou a následnou ASCT. Při přetrvávající pozitivitě PET/CT po úvodním záchranném režimu lze zvážit další léčbu s cílem prohloubit léčebnou odpověď, například změnou chemoterapeutického režimu nebo zařazením brentuximab vedotinu či inhibitoru PD-1. Volba dalšího postupu by měla vycházet z rozsahu reziduálního onemocnění, předchozí léčby a celkového klinického stavu pacienta.^{55,61,63}

Zařazení inhibitorů kontrolních bodů imunitní odpovědi, zejména nivolumabu a pembrolizumabu, do léčby HL přineslo specifické výzvy v interpretaci PET/CT. Imunoterapie může v důsledku aktivace imunitní odpovědi vést k přechodnému zvětšení nádorových lézí nebo ke zvýšení jejich metabolické aktivity spojenému se zvýšenou akumulací ¹⁸F-fluorodeoxyglukózy. Tyto změny mohou napodobovat progresi onemocnění a vést k fenoménu tzv. pseudoprogrese. Pro hodnocení těchto atypických léčebných odpovědí byla vytvořena kritéria LYRIC (Lymphoma Response to Immunomodulatory Therapy Criteria), která zavádějí kategorii neurčité odpovědi a doporučují další hodnocení vývoje nálezu.⁶⁴ Kombinace brentuximab vedotinu s nivolumabem dosáhla ve studii fáze I/II vysoké četnosti léčebných odpovědí a umožnila většině vhodných pacientů následně podstoupit ASCT.^{61,65-67}

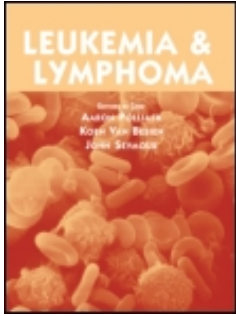
Cílem následující retrospektivní studie, bylo především zhodnotit prognostický význam PET vyšetření před ASCT u pacientů s relabujícím nebo refrakterním HL a porovnat jeho prediktivní význam se sekundárním klinickým rizikovým skóre při relapsu a s dosažením kompletní remise hodnocené pomocí CT po záchranné chemoterapii. Studie prokázala, že negativní PET nález před ASCT byl spojen s příznivějšími léčebnými výsledky. Pacienti s negativním PET dosahovali významně vyššího dvouletého přežití bez progrese i celkového přežití než pacienti s pozitivním PET nálezem. Výsledky tak podpořily význam metabolické odpovědi před ASCT jako prognostického ukazatele umožňujícího identifikovat pacienty s vyšším rizikem nepříznivého průběhu po transplantaci.

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ORIGINAL ARTICLE: CLINICAL

Pre-transplant positron emission tomography in patients with relapsed Hodgkin lymphoma

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Abstract

This retrospective study evaluated the secondary clinical risk score at relapse, the prognostic significance of pre-transplant positron emission tomography (PET), and complete remission (CR) assessed by computed tomography (CT) after salvage chemotherapy before autologous stem cell transplant (ASCT) in 76 patients with relapsed/refractory Hodgkin lymphoma (HL). Median follow-up after ASCT was 23 months. Overall 11/20 PET-positive and 14/56 PET-negative patients relapsed after ASCT. In univariate analysis, only PET negativity before ASCT was significantly associated with better 2-year progression-free survival (PFS) ($72.7 \pm 6.3\%$ vs. $36.1 \pm 11.6\%$, $p = 0.01$) and 2-year overall survival (OS) ($90.3 \pm 4.1\%$ vs. $61.4 \pm 11.6\%$, $p = 0.009$). Other factors were not significant. In multivariate analysis, none of the evaluated factors were significant for PFS and OS. However, positive pre-transplant PET identified a population with worse PFS and OS at least in univariate analysis.

Keywords: Hodgkin lymphoma, PET, autologous stem cell transplant

Introduction

Second-line salvage chemotherapy followed by autologous stem cell transplant (ASCT) has become the standard of treatment in patients with relapsed Hodgkin lymphoma (HL); however, it cures only half of them. Several studies have analyzed adverse prognostic factors at relapse of HL to predict the outcome after ASCT [1,2]. The German Hodgkin Study Group (GHSG) defined a secondary clinical risk score for relapsed HL based on the outcomes of 422 patients with relapsed HL. Multivariate analysis indicated three independent risk factors: time to relapse (<12 vs. >12 months), clinical stage at relapse (stage III/IV), and anemia at relapse (males,

hemoglobin [Hb] <12 g/dL; females, Hb <10.5 g/dL). Freedom from second failure (FF2F) rates were estimated at 45%, 32%, and 18% for patients with 0/1, 2, and 3 prognostic factors, respectively [2]. Response to salvage chemotherapy prior to ASCT is the most important prognostic factor associated with the outcome of patients with relapsed HL [3]. Computed tomography (CT) scans have their limitations, especially in patients with residual masses after treatment, where they cannot distinguish between a scar and a residual tumor in HL. [^{18}F]2-fluoro-D-2-deoxyglucose-positron emission tomography (^{18}F -FDG-PET) is currently recommended in initial staging and for evaluation of response at the end of first-line therapy in patients

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There is an accompanying commentary that discusses this paper. Please refer to the issue Table of Contents.

with diffuse large B-cell lymphoma (DLBCL) and HL [4]. The predictive role of PET scans in the pre-transplant setting has been assessed in several studies with non-Hodgkin lymphoma (NHL) and HL and correlated well with the post-transplant outcome [5–10]. The reported event-free survival (EFS) rate was 54–83% for PET-negative patients and 7–43% for PET-positive patients [5,6,11–13]. Studies with chemoresistant PET-positive patients resulted in median progression-free survival (PFS) of less than 4 months after ASCT [5–8,14]. Pre-transplant PET was more predictive of outcome in patients with HL compared to DLBCL according to the study by Crocchiolo *et al.* [15]. Based on a systematic review and meta-analysis of pre-transplant PET in 630 patients with NHL or HL, ^{18}F -FDG-PET had a summary sensitivity of 0.69 (95% confidence interval [CI] 0.56–0.81) and specificity of 0.81 (95% CI 0.73–0.87) [16]. Schot *et al.* developed a risk model for combined use of the clinical risk score and PET response after two cycles of salvage chemotherapy in patients with NHL and HL [11]. Both secondary clinical risk score ($p < 0.001$) and PET response ($p < 0.001$) were independent predictive factors. Patients were stratified into four risk subgroups that predicted more accurate outcome after ASCT, ranging from 80–100% responses in a subgroup with a low combined risk score to 0–7% responses in a subgroup with a high combined risk score [2,11,17]. Although the prognostic value of PET scans prior to ASCT for relapsed lymphomas seems to be better clarified, there appears to be little consensus on the use of the scan results.

Conflicting results have been reported on the correlation between PET after ASCT and long-term clinical outcome in patients with HL and NHL [18,19].

This retrospective study evaluated the GHSG secondary clinical risk score at relapse, the prognostic significance of PET, and achievement of complete remission (CR) assessed by CT after salvage chemotherapy before ASCT in 76 patients with relapsed/refractory HL.

Patients and methods

Patients

Relapse/progression of HL was confirmed by biopsy and CT in 76 patients between 2000 and 2009. All these patients underwent pre-transplant PET after second-line chemotherapy before ASCT. The characteristics of the 76 patients are summarized in Table I. Prognostic factors were assessed at relapse and analyzed in 70 patients according to the GHSG secondary clinical risk score [2]. The prognostic

Table I. Characteristics of patients with Hodgkin lymphoma ($n = 76$).

Gender: male/female	40/36
Age at ASCT, median (range) (years)	34 (20–61)
Clinical risk factors at relapse (n)	
Primary refractory HL	6
Relapse < 12 months after first-line therapy	16
Anemia at relapse (males, Hb < 12 g/dL; females, Hb < 10.5 g/dL)	12
Ann Arbor clinical stage at relapse (n)	
I/II	26
III/IV	50
GHSG secondary clinical risk score at relapse (n)	
0,1	52
2	16
3	2
Unknown prognostic score	6
Second-line therapy prior to ASCT (no. of cycles, range) (n)	
DHAP, ESHAP (2–4)	41
ICE (2–6)	15
CEVD (2–4)	10
ABVD (4–6)	6
Gemcitabine alone (2)	2
IVE (4)	2
PET after salvage chemotherapy (no. of cycles) (n)	
2	32
3	19
4	16
5	5
6	4

ASCT, autologous stem cell transplant; HL, Hodgkin lymphoma; Hb, hemoglobin; GHSG, German Hodgkin Study Group; PET, positron emission tomography; DHAP, dexamethasone, cytarabine, cisplatin; ESHAP, etoposide, cytarabine, cisplatin, methylprednisolone; ICE, ifosfamide, carboplatin, etoposide; CEVD, lomustine, etoposide, vindesine, dexamethasone; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; IVE, ifosfamide, epirubicin, etoposide.

score was not evaluated in six patients with primary refractory HL. Patients received various types of salvage chemotherapy. The choice of salvage regimens and the number of cycles (median 3 cycles) depended on decisions taken at the individual centers (Table I). Decisions were made on the basis of clinical response to salvage chemotherapy. Results of the pre-transplant assessment including PET did not impact the decision to proceed to transplant. Overall, 72 patients underwent single ASCT after the conditioning regimen BEAM (carmustine, etoposide, cytarabine, melphalan) and four patients were treated with tandem ASCT: the first conditioning regimen consisted of melphalan and mitoxantrone and BEAM was used for the second conditioning. Involved field radiotherapy was performed in patients with PET positivity and/or with a residual post-transplant tumor (≥ 2.5 cm assessed by CT) in

previously not irradiated sites 3 months after ASCT. The radiation doses varied between 30 and 40 Gy. Out of 76 patients, 32 were irradiated after ASCT, including nine PET-positive patients.

Restaging assessment

Conventional restaging methods included: physical examination, laboratory studies, chest X-ray, CT and/or ultrasound of the neck, CT of the chest, abdomen, and pelvis, and magnetic resonance imaging in selected cases. The timings of restaging were: at the first relapse, after salvage chemotherapy prior to ASCT, 3 months after ASCT, and in subsequent relapse. Responses after treatment and relapses were evaluated according to the International Working Group criteria for response assessment of lymphoma [20].

PET studies

Overall, 42 FDG-PET and 34 FDG-PET/CT studies were carried out after second-line chemotherapy, 2–6 weeks before ASCT, and no additional treatment was offered to these patients between PET and ASCT (Table I). Additionally, 54 PET scans were performed 3 months after ASCT, and post-transplant PET was not performed in 22 patients. PET and PET/CT studies were conducted at three PET centers with one of the following scanners: whole-body PET scanner ECAT EXACT BGO Siemens; PET/CT scanner Biograph Duo LSO Siemens MS; Siemens Biograph TruePoint PET/CT scanner with 64-slice CT; and PET/CT scanner Siemens Biograph 16. Patients fasted for at least 4–6 h before the study. Serum glucose levels were obtained before the scans to document euglycemia. Scans were obtained 60–90 min after the intravenous administration of a dose of ^{18}F -FDG adjusted to body weight (350–550 MBq). Sequential overlapping scans were acquired to cover from the base of the skull to the mid-thighs, including the neck, chest, abdomen, and pelvis. PET and PET/CT studies were evaluated visually by local nuclear medicine specialists at the time of the scan, and scans were not centrally reviewed. The standardized uptake value was not used for the evaluation of PET. In cases of separate PET and CT scans, these data were not merged. Positive PET scans were defined as areas with increased FDG uptake above background, concordant with a tumor [21]. PET scans were interpreted as negative when no evidence of increased FDG uptake above background was revealed. PET results did not impact the decision to perform ASCT.

Statistics

PFS was defined as the time interval from ASCT until the first objective evidence of relapse/progression or date of the last follow-up. Overall survival (OS) was calculated from the date of ASCT until lymphoma-related death or death from any other cause. Survival curves were calculated by Kaplan–Meier analysis and comparison between subgroups was performed by the log-rank test. Factors analyzed in the univariate analysis were: primary refractory HL, the GHSG secondary clinical risk score at relapse, achievement of complete remission after salvage chemotherapy assessed by CT, and pre-transplant PET scans. Multivariate analysis by proportional hazards (Cox) regression was performed to evaluate the significance of the GHSG secondary clinical risk score at relapse, achievement of complete remission after salvage chemotherapy according to CT, and pre-transplant PET findings on PFS and OS. STATISTICA software (StatSoft Inc., Tulsa, OK) was used for statistical analyses.

Results

PET was performed in 76 patients with relapsed/progressed HL after salvage chemotherapy prior to ASCT with the following results: there were 20 PET-positive patients (26.3%) and 56 PET-negative patients (73.7%). PET and CT restaging assessment after salvage chemotherapy is summarized in Table II: 1/30 patients in complete remission (CT) remained PET-positive and 16/37 patients in partial remission (CT) were PET-positive. Three out of nine patients with stable or progressive disease remained PET-positive before ASCT. Five of six primary refractory patients with HL achieved PET negativity (one complete remission, two partial remissions, two stable diseases assessed by CT) after salvage chemotherapy and none of them relapsed after ASCT: four are in complete remission and one in partial remission (CT findings). One primary

Table II. Response to salvage treatment in patients with Hodgkin lymphoma prior to ASCT ($n = 76$).

Response	Number of patients		
	CT	PET negative	PET positive
Complete remission (un)confirmed	30	29	1
Partial remission	37	21	16
Stable disease	5	4	1
Progression/relapse	4	2	2
Total	76	56	20

CT, computed tomography; PET, positron emission tomography.

refractory patient remained PET-positive after salvage chemotherapy and died due to HL progression after ASCT. The risk of death was 3.5 times higher in our PET-positive patients when compared to PET-negative patients. Out of 51 patients treated with two or three cycles of salvage chemotherapy, 11 remained PET-positive and nine of 25 patients treated with more than three cycles of chemotherapy were PET-positive prior to ASCT; the difference between both groups was not significant ($p = 0.29$).

During the median follow-up of 23 months (range 3–108), overall 11 (55%) of 20 PET-positive patients and 14 (25%) of 56 PET-negative patients relapsed after ASCT. The negative predictive value of pre-transplant PET was 75% and the positive predictive value was 55%. Relapses/progressions after ASCT were documented in 25 (33%), including five relapses in pre-transplant PET-positive sites and eight with positive post-transplant PET.

Out of 32 patients irradiated after ASCT, 11 relapsed, including six relapses in the irradiated fields.

Overall, 19 of 76 (25%) patients died: 11 in relapse/progression of HL and eight patients due to non-relapse mortality (five transplant-related mortalities, one cardiac failure, one pulmonary embolism, one ischemic stroke).

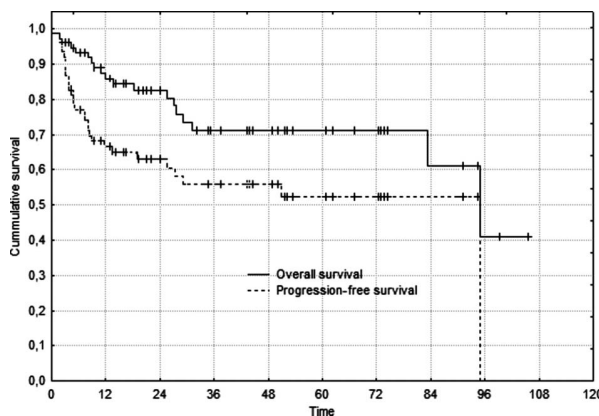


Figure 1. PFS and OS of patients with Hodgkin lymphoma ($n = 76$).

The 2-year PFS of 76 patients with HL was 63.1% (95% CI 51.7–74.5%) and OS 82.5% (95% CI 73.5–91.5%) (Figure 1). The median follow-up of living patients was 33.6 months (range 3.2–105.8).

Univariate analysis

Primary refractory disease compared to relapsed HL was not significantly associated with worse PFS ($p = 0.933$, hazard ratio [HR] = 0.94) or OS ($p = 0.27$, HR = 2.31) (Table III). The GHSG secondary clinical risk score 2 or 3 at HL relapse was not significantly associated with worse PFS ($p = 0.066$, HR = 2.08) and OS ($p = 0.878$, HR = 1.08). The response to salvage chemotherapy (complete remission vs. no complete remission) assessed by CT was not significant in terms of PFS ($p = 0.073$, HR = 0.5) and OS ($p = 0.116$, HR = 0.46). Differences in PFS between PET-negative and PET-positive patients were statistically significant (Figure 2): the estimated 2-year PFS for PET negative patients was 72.7% (95% CI 60.4–85%) and for PET-positive patients 36.1% (95% CI 13.4–58.8%), $p = 0.01$, HR = 2.68. Differences in OS between PET-positive and PET-negative subgroups were statistically significant (Figure 3): the estimated 2-year OS for PET-positive patients was 61.4% (95% CI 38.7–84.1%) and for PET-negative patients 90.3% (95% CI 82.3–98.3%), $p = 0.009$, HR = 3.47.

Multivariate analysis

The Cox model was used for PFS and OS analysis of three variables: high GHSG risk score, PET positivity, and CR assessed by CT before ASCT (Table IV). Six patients with primary refractory disease were excluded from the multivariate analysis. In the multivariate analysis, none of these factors were statistically significant for PFS. PET was significant for PFS only in combination with other variables (the GHSG secondary clinical risk score at relapse and CR assessed by CT), $p = 0.017$. Cox regression analysis for OS of three variables (high GHSG risk

Table III. Univariate analysis of risk factors for progression-free and overall survival ($n = 76$).

Risk factors	Progression-free survival			Overall survival		
	HR	95% CI	p -Value	HR	95% CI	p -Value
GHSG secondary clinical risk score at relapse 2 or 3	2.08	0.95–4.56	0.066	1.08	0.38–3.05	0.878
PET positivity	2.67	1.27–5.62	0.010	3.46	1.36–8.77	0.009
CR according to CT	0.49	0.22–1.06	0.073	0.45	0.17–1.21	0.116
Primary refractory	0.94	0.22–3.95	0.933	2.31	0.22–3.15	0.270

HR, hazard ratio; CI, confidence interval; GHSG, German Hodgkin Study Group; PET, positron emission tomography; CR, complete remission; CT, computed tomography.

score, PET positivity, CR according to CT prior to ASCT) was not statistically significant.

Discussion

We have evaluated the GHSG secondary clinical risk score at relapse, the prognostic significance of PET, and achievement of CR assessed by CT after salvage chemotherapy before ASCT in a group of 76 patients with relapsed/refractory HL. In our cohort, 11 (55%) of 20 PET-positive patients with HL relapsed and 14 (25%) of 56 PET-negative patients with HL

relapsed. Our data are comparable with the data reported by Jabbour *et al.* on 68 patients with HL with pre-transplant PET: 18 (72%) of 25 PET-positive patients relapsed and 10 (23%) of 43 PET-negative patients relapsed [22]. Jabbour *et al.* also documented the presence of B symptoms, lack of complete remission at ASCT, PET results, and conditioning regimen BEAM as independent predictive factors for PFS, and complete remission, radiation therapy, and BEAM were independently predictive for OS. According to our data, PET positivity was the only predictive factor for PFS and OS in univariate analysis ($p=0.01$ and $p=0.009$, respectively), and these observations support the results of the study published by Spaepen *et al.*, where pre-transplant PET was the only prognostic factor associated with PFS [6]. The GHSG secondary clinical risk score at relapse and achievement of CR after salvage chemotherapy according to CT failed to show a statistical significance in our study, and this observation should be viewed with caution as the number of evaluated patients was low.

In our multivariate analysis, PET was not significant for PFS and OS due to the correlation between all variables in the analysis. Our results differ from those of other studies, where PET was an independent prognostic factor in multivariate analyses [6,21,22]. This difference may be due to the few events occurring in our trivariate analysis.

Five of our six primary refractory patients with HL achieved PET negativity prior to ASCT, and none of them relapsed after ASCT. This probably reflects a resistance to the first-line chemotherapy but not overall resistance to the salvage therapy. Primary refractory HL was not proved to be a significant risk factor for PFS or OS in our univariate analysis. One patient with primary refractory disease with PET positivity, although in complete remission according to CT before ASCT, subsequently relapsed. No definitive conclusion can be drawn from such a small group of patients. Svoboda *et al.* demonstrated that a small group of chemoresistant patients with negative PET scans experienced prolonged PFS, which was comparable to those with chemosensitive disease and negative PET scans [5].

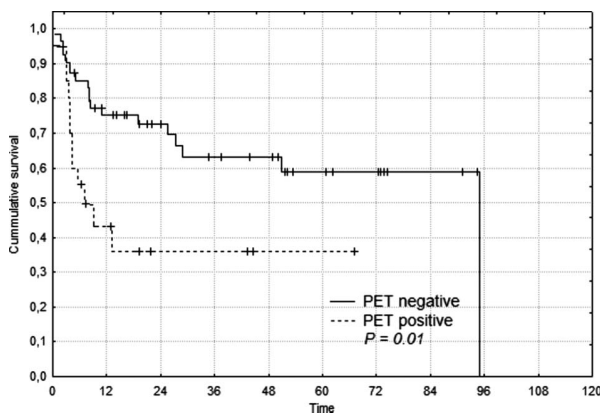


Figure 2. PFS according to PET results.

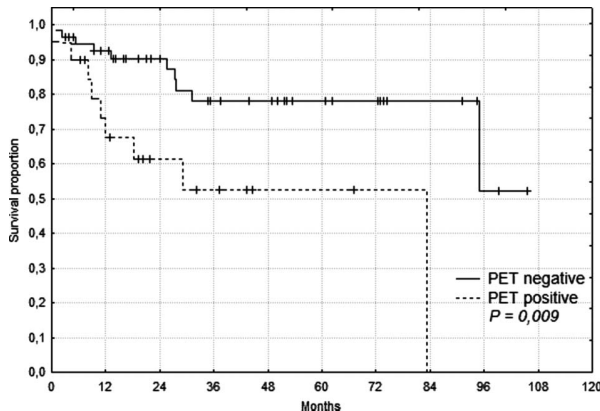


Figure 3. OS according to PET results.

Table IV. Multivariate analysis of risk factors for progression-free and overall survival ($n=70$).

Risk factors	Progression-free survival			Overall survival		
	HR	95% CI	<i>p</i> -Value	HR	95% CI	<i>p</i> -Value
GHSG secondary clinical risk score at relapse 2 or 3	2.02	0.88–4.62	0.094	0.97	0.33–2.89	0.968
PET positivity	1.78	0.76–4.14	0.177	2.73	0.96–7.73	0.057
CR according to CT	0.49	0.21–1.15	0.105	0.55	0.18–1.67	0.293

HR, hazard ratio; CI, confidence interval; GHSG, German Hodgkin Study Group; PET, positron emission tomography; CR, complete remission; CT, computed tomography.

Out of our 56 PET-negative patients, 14 relapsed after ASCT, and this finding supports the observation that even a negative PET scan cannot exclude a late relapse.

The optimal timing of PET before transplant is currently unknown. Patients included in our analysis underwent only one PET scan before ASCT, although the number and type of second-line chemotherapy cycles varied. Number of salvage chemotherapy cycles (2–3 vs. more than 3) was not significant for PET response ($p = 0.29$). Schot *et al.* analyzed PET scans in 39 patients with relapsed lymphoma (28 with aggressive NHL and 11 with HL) after two cycles of second-line chemotherapy and after a third cycle of chemotherapy before ASCT in cases with abnormal PET after two cycles. PET after three cycles had a slightly better predictive accuracy than PET after two cycles, especially for identifying those patients who would have a poor prognosis [23]. Most patients with persistent PET positivity were refractory to therapy, and they progressed or relapsed soon after ASCT.

The risk of death was 3.5 times higher in our PET-positive patients when compared to PET-negative patients. According to a meta-analysis of pre-transplant PET in patients with lymphoma, the risk of progression is three times higher while the risk of death is four times higher in patients not achieving a pre-transplant PET-negative scan [24]. We assume that PET positivity after salvage chemotherapy is not an absolute contraindication for ASCT, as it was effective in nine of our 20 PET-positive patients. Moskowitz *et al.* reported one-third of patients with abnormal pre-ASCT functional imaging who were cured by ASCT, and supported the theory that ASCT remains the standard of treatment [25]. However, PET-positive patients are at a higher risk of relapse or progression after ASCT. Radiotherapy can be used before and after ASCT and as a part of a conditioning regimen. Radiotherapy alone is a reasonable approach in selected patients. This is supported by a retrospective analysis of 100 patients with relapsed disease in localized stages and without risk factors treated with radiotherapy alone [26]. In this group, 77% had a CR, 51% were alive at 5 years, and 28% were disease-free at 5 years. Whereas the 5-year OS rate was 68% in patients with stage I disease, it was only 27% for those with stage III/IV disease. Moskowitz *et al.* conducted a phase II intent-to-treat study with augmented or high dose ICE (ifosfamide, carboplatin, etoposide) in patients with relapsed/refractory HL and risk factors [10]. Chemosensitive patients evaluated by functional imaging (gallium or FDG-PET scan) underwent combined high-dose chemoradiotherapy (either as total lymphoid irradiation or as an involved field) and ASCT. Pre-ASCT functional imaging predicted outcome: 4-year EFS rates were 33% vs.

77% for patients transplanted with positive versus negative functional imaging, respectively, $p = 0.00004$. The authors suggested that patients not achieving functional imaging negativity after salvage chemotherapy require additional non-cross-resistant treatment to further cytoreduce disease burden prior to ASCT, including intensity-modulated radiation therapy. Morschhauser *et al.* reported a benefit of tandem ASCT with total-body irradiation as part of a second conditioning regimen for patients with poor-risk HL, chemotherapy-resistant or partial responders [27]. Radiotherapy was offered to 32 patients after ASCT in our study, but despite irradiation, 11 of them relapsed, including six relapses in the irradiation fields, and radiotherapy had no significant impact on PFS or OS ($p = 0.966$ and $p = 0.997$, respectively). No definitive conclusion can be drawn from this small and heterogeneous cohort of patients treated with radiation after ASCT. New drugs, e.g. histone deacetylase or mammalian target of rapamycin (mTOR) inhibitors and the most promising antibody–drug conjugates (SGN-35) are currently being tested in high-risk HL after ASCT. In summary, positive pre-transplant PET identified a population with worse PFS and OS at least in univariate analysis. Treatment decisions based on PET results remain to be defined.

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6. Extranodální postižení u Hodgkinova lymfomu a jeho prognostický význam

U HL převažuje nodální způsob šíření onemocnění, zatímco extranodální manifestace je méně častá než u řady ne-Hodgkinových lymfomů. Přítomnost extranodálního postižení má význam zejména pro stanovení klinického stadia, prognostickou stratifikaci a volbu léčebného postupu.^{66,68}

V rámci Ann Arbor klasifikace, modifikované podle Luganské klasifikace, je nutné rozlišovat mezi přímým šířením nádoru z postižené lymfatické uzliny do bezprostředně přilehlé extranodální tkáně a vzdáleným extranodálním postižením. Stadium IV je definováno diseminovaným postižením jednoho nebo více extranodálních orgánů, které není vysvětlitelné přímým šířením z regionálně postižených lymfatických uzlin.^{12,64,68}

Extranodální postižení se nejčastěji vyskytuje u pacientů s pokročilým onemocněním a může postihovat řadu orgánů, zejména plíce, játra, kostní dřeň a skelet. Vzhledem k častému postižení mediastinálních uzlin může být plicní nález také důsledkem přímého prorůstání mediastinálního tumoru do plicního parenchymu. Postižení kostní dřeně je typicky spojeno s pokročilým onemocněním a dalšími nepříznivými klinickými charakteristikami, včetně B-symptomů, anémie a leukopenie.⁶⁸⁻⁷⁰ Jaterní postižení se rovněž vyskytuje především u pokročilého diseminovaného onemocnění. Nález primární extranodálního HL bez současného postižení lymfatických uzlin je velmi vzácný.⁶⁸

Vyšetření PET/CT zásadně zvýšilo přesnost stanovení rozsahu onemocnění HL a umožnilo spolehlivější detekci extranodálních lézí. PET/CT má také vysokou senzitivitu pro průkaz metabolicky aktivního postižení kostní dřeně, a proto u nově diagnostikovaných pacientů s HL při dostupnosti kvalitního PET/CT vyšetření není rutinní biopsie kostní dřeně již obecně indikována. Výjimkou mohou být nejednoznačné nálezy nebo situace, kdy by histologické ověření mělo význam pro diagnostiku či léčebný postup.^{2,69-71}

Z prognostického hlediska je extranodální postižení spojeno zejména s pokročilejším onemocněním a v některých souborech také s horšími léčebnými výsledky. Je však nutné odlišovat samotnou přítomnost extranodálního postižení od jeho prognostického významu v rámci jednotlivých klinických situací. U pokročilého HL je základním historickým prognostickým nástrojem International Prognostic Score (IPS), jehož

součástí je sedm nepříznivých faktorů: mužské pohlaví, věk ≥ 45 let, stadium IV, albumin < 40 g/l, hemoglobin < 105 g/l, leukocytóza $\geq 15 \times 10^9/l$ a lymfopenie $< 0,6 \times 10^9/l$ nebo < 8 % leukocytů. Extranodální postižení tedy není samostatnou součástí IPS.²⁶

Význam extranodálního postižení může být dále ovlivněn jeho rozsahem a lokalizací. Postižení kostní dřeně představuje manifestaci pokročilého onemocnění a je spojeno s některými dalšími nepříznivými klinickými charakteristikami. Vassilakopoulos et al. identifikovali jako prediktory postižení kostní dřeně zejména B-symptomy, stadium III/IV, anémii, leukopenii, vyšší věk a postižení inguinálních či ilických lymfatických oblastí.⁷⁰ Prognostický význam jednotlivých extranodálních lokalizací však není jednotný a měl by být posuzován v kontextu celkového rozsahu onemocnění a dalších rizikových faktorů.^{14,72}

Předložená retrospektivní studie měla za cíl podrobněji posoudit prognostický význam extranodálního postižení u HL a zjistit, zda se léčebné výsledky liší v závislosti na konkrétní lokalizaci extranodálního postižení. Analýza souboru 855 nemocných s HL ukázala, že přítomnost extranodálního postižení byla spojena s významně horším přežitím bez progresu i celkovým přežitím, přičemž nejméně příznivý průběh byl pozorován u nemocných s jaterním postižením. Studie tak přispěla k přesnějšímu vymezení prognostického významu extranodálního postižení a ukázala, že jeho prognostický dopad není uniformní, ale může se lišit podle rozsahu a konkrétní lokalizace postižené tkáně. Tyto poznatky podporují potřebu zohlednění charakteru extranodálního postižení při stratifikaci rizika a individualizaci léčebného přístupu u nemocných s HL. Podrobnosti jsou uvedeny v následující vložené publikaci.

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Extranodal Involvement in Hodgkin's Lymphoma: A Retrospective Analysis of Survival Outcomes and Prognostic Factors at a Single-Center Study

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Abstract

Extranodal involvement in Hodgkin's lymphoma (HL) indicates advanced disease and may negatively impact survival. This study aimed to evaluate the influence of extranodal involvement on progression-free survival (PFS) and overall survival (OS) and to identify prognostic factors related to extranodal site involvement. This retrospective study analyzed 855 HL patients treated at a single oncology center from 2003 to 2020. Extranodal involvement was identified using imaging (CT, PET/CT, MRI) and biopsy. Survival outcomes were assessed with Kaplan-Meier estimates, and Cox regression was used to evaluate prognostic factors for PFS and OS. Extranodal involvement was present in 181 patients, most commonly affecting the lungs, bone, liver, and chest wall. Extranodal involvement significantly reduced both PFS and OS in patients ($p < 0.02$ for PFS; $p < 0.001$ for OS). The worst survival among 181 patients with extranodal involvement was observed in patients with liver involvement ($p = 0.004$ for PFS; $p < 0.033$ for OS). Conversely, localized involvement of extralymphatic sites showed better survival outcomes ($p < 0.009$ for PFS; $p < 0.011$ for OS). Age, gender, clinical stage, and radiotherapy were independent survival predictors. Extranodal involvement, particularly in the liver, is associated with poorer outcomes in HL patients. These results emphasize the importance of tailoring treatment strategies based on the specific sites of extranodal disease.

Keywords Hodgkin's lymphoma · Extranodal disease · Overall survival · Progression-free survival

1 Introduction

Hodgkin's lymphoma (HL) is a malignant tumor that arises primarily in the lymphatic system. Although the exact etiology of this disease has not yet been fully elucidated, it is

certain that a combination of genetic, environmental, and immunological factors are involved. Remarkably, individuals with a family history of HL have a slightly higher risk of developing the disease. In addition, a weakened immune system, whether due to inherited diseases, HIV/AIDS or immunosuppressive drugs, is considered a risk factor. Certain herpes viruses have also been associated with an increased risk of Hodgkin's lymphoma, particularly in young adults [1–4].

The therapeutic approach for HL has evolved considerably over the years and currently a combination therapy including chemotherapy and radiotherapy is the standard treatment of choice. The choice between these modalities depends on a variety of factors, including the stage of the disease, the age of the patient, and his or her performance status. In recent years, the options have expanded, particularly in the field of targeted therapy and immunotherapy. Monoclonal antibodies such as rituximab have shown

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efficacy by specifically targeting tumor cells - particularly in the nodular lymphocyte predominant HL, while immunotherapies such as checkpoint inhibitors like nivolumab and pembrolizumab have shown promise in the treatment of refractory or relapsed Hodgkin lymphoma. In addition, stem cell transplantation may be considered in some cases and offers a potentially curative option [5–7].

HL has a generally favourable prognosis, especially when diagnosed at an early stage. Five-year survival rates for Hodgkin lymphoma exceed 80% and many patients achieve long-term remission or are considered cured. However, the prognosis varies depending on factors such as the stage at the time of diagnosis, the presence of certain risk factors and the patient's performance status.

HL mainly affects lymph nodes, most often supradiaphragmatic. Extranodal involvement is observed more frequently in non-Hodgkin's lymphoma [8]. Extranodal involvement in HL often indicates advanced disease. The frequency of extranodal involvement is less common in HL and ranges from 15% to 30% of cases [9]. The presence of extranodal involvement also poses a challenge in the management of HL patients. Although less common than lymph node disease alone, extranodal manifestations can significantly affect the therapeutic approach and survival of patients [4, 10–13].

Therefore, the aim of this study was to evaluate the survival of a large consecutive cohort of HL patients treated at our institution, both in relation to the presence of extranodal involvement in general and with respect to the specific site affected. Furthermore, we aimed to identify factors that stratify patients into low- and high-risk groups with respect to recurrence and overall prognosis. Such stratification may be clinically relevant for optimizing therapeutic strategies, as patients with high-risk features could benefit from more intensive treatment approaches, while those with favorable prognostic profiles might be considered for less intensive regimens in order to minimize treatment-related toxicity. In this context, improved risk stratification could help to avoid both under-treatment of high-risk patients and unnecessary over-treatment of low-risk individuals.

2 Patients and Methods

2.1 Patients

This study consecutively enrolled 855 patients treated at the Department of Internal Medicine, Hematology and Oncology at University Hospital Brno in the period 2003–2020. Subjects older than 15 years of age with histological evidence of newly diagnosed HL were eligible for the study. The ratio of men and women enrolled corresponds to the

normal incidence of the disease. Patients were followed up until May 2020, for at least 3 years. The median follow up of all patients enrolled in the study is 5.6 years (patients with/without extranodal involvement 5.0/5.8 years). On June 1, 2020, the data were accessed for research purposes. The authors did not have access to information that could identify individual study participants.

As the relevant pilot data were not available prior to the statistical analyses and this is a real-world evidence study, a formal power analysis could not be performed in advance. The study was discussed with our institutional ethics committee. It was conducted according to the guidelines of the Declaration of Helsinki and other applicable international standards and regulations that protect human rights, dignity, safety of research participants and ensure scientific integrity.

Assessment of treatment response was performed for patients who had not undergone PET scanning according to 2007 criteria, and for patients who had undergone PET scanning according to 2014 criteria [14–16]. Overall survival (OS) was defined as the interval from the date of diagnosis to the death from any cause. All enrolled patients were diagnosed by at least two experienced pathologists. Demonstration of extranodal involvement was based on contrast-enhanced computed tomography (CT), positron emission tomography-CT (PET/CT) or magnetic resonance imaging (MRI) in combination with biopsy, and then assessed by clinicians.

Patients in our cohort were treated according to the protocols of the German Hodgkin's Study Group (GHSG); initial therapy for localized stages was based on ABVD and IF RT, for intermediate stages on ABVD or a combination of ABVD and BEACOPP regimens supplemented with IF RT, depending on the presence of risk factors. Advanced stages were treated with BEACOPP escalated; RT was performed only in patients with active residual after completion of chemotherapy. Patients who did not achieve a complete remission after initial therapy or were shown to have relapsed classical Hodgkin lymphoma (cHL) were referred for autologous hematopoietic cell transplantation. A total of 61 patients received salvage therapy, 2 cycles of DHAP or ICE, followed by high-dose BEAM chemotherapy followed by autologous bone marrow transplantation. Chemotherapy regimens: ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine), BEACOPP (Cyclophosphamide, Adriamycin, Etoposide, Procarbazine, Prednisone, Vincristine), DHAP (cisPlatinum, Cytosar, Dexamethasone), ICE (Ifosfamide, Carboplatin, Vepesid), BEAM (Carmustine, Cytosar, Etoposide, Melphalan).

The median age of patients at diagnosis was 37 years (27 years, 56 years; 25% and 75% quantile, respectively). Five-year survival was achieved in 87.1% of patients (0.847–0.896; 95% Confidence Interval), and 15-year survival was

Table 1 Clinicopathological characterization of the whole patient cohort

Monitored parameter		N=855	%
Clinical stage	I	66	7.72
	II	411	48.07
	III	221	25.85
	IV	154	18.01
	NA	3	0.35
Gender	F	394	46.08
	M	461	53.92
Radiotherapy	Yes	404	47.25
	No	430	50.29
	NA	21	2.46
Stem cell transplantation	Yes	61	7.14
Chemotherapy Type	Yes	855	100
	Nodular Sclerosing	467	54.62
	Mixed Cellularity	254	29.71
	Lymphocyte Rich	59	6.90
	NLPHL	32	3.74
	Lymphocyte Depleted	13	1.52
Extranodal involvement	Yes	181	21.17
	No	674	78.83
Number of extranodal involvements	1	131	72.38
	2	40	22.10
	3 and more	10	5.52

Table 2 Anatomical localization of extranodal involvement in 181 HL patients

Localization	N*	%
Grow from anywhere around	56	18
Lung	77	25
Pleura	5	2
Liver	36	12
Oesophagus	2	1
Kidneys	2	1
Skeleton	41	13
Bone marrow	20	7
Pericardium	2	1
Breast	2	1
Chest wall	34	11
Muscle	8	3
Pancreas	2	1
Thyroid gland	2	1
Other	15	5

*The table lists both unique and concurrent instances of intranodal involvement in various anatomical regions. A total of 304 such instances were identified in the cohort

Table 3 PET/CT scans and extranodal involvement

	Extranodal HL	Non extranodal HL	p-value
No. of patients	181	674	
PET/CT	62 (15.8%)	330 (84.2%)	0.229
Non PET/CT	88 (19.0%)	375 (81.0%)	

Table 4 Presence of extranodal involvement in patients at different clinical stages of the disease

Extranodal disease	Clinical stage		
	I	II	III+IV
Yes	2	25	154
No	64	386	221

achieved in 76.7% of patients (0.725–0.810; 95% CI). A more detailed summary of the clinicopathological data of the enrolled patients is summarized in Table 1.

2.2 Statistical Analysis

All statistical analyses were performed in R [17] and its additional package survival [18]. Statistical significance was set at level $\alpha = 0.05$. Univariate and multivariate Cox regression models were applied in order to confirm the effect of specific predictors on overall and progression-free survival. Kaplan-Meier curves were used for visualizations of survival data. The χ^2 test was used to determine the difference in the proportion of PET scans and extranodal involvement.

3 Results

Of the total consecutive cohort evaluated, extranodal involvement was present in 181 (21.17%) patients (Table 2). Of the 855 patients, 392 (45.8%) were examined by PET/CT. There was no significant difference in the incidence of extranodal involvement in patients who underwent PET/CT compared to patients who did not undergo PET/CT (Table 3). The median age of patients with extranodal involvement at diagnosis was 41 years (29 years, 60 years; 25% and 75% quantile, respectively). Five-year survival was achieved in 78.9% of patients (0.728–0.856; 95% CI), and 15-year survival was achieved in 69.3% of patients (0.604–0.795; 95% CI).

Extranodal involvement occurred in our cohort with high significance mainly in patients in clinical stage IV ($p < 2.2 \times 10^{-16}$; Fisher exact test). Furthermore, sporadic occurrence was observed in patients in clinical stages I and II (Table 4).

By statistics evaluating our clinical data, we further demonstrated that extranodal manifestation significantly impaired PFS ($p < 0.02$, logrank test; HR = 1.461, 95% CI 1.062–2.012) and OS ($p < 0.00023$, logrank test; HR = 1.999, 95% CI 1.383–2.890) in HL patients (Fig. 1).

Of all the observed and evaluated extranodal lesions, liver involvement significantly worsens PFS ($p = 0.004$, HR = 2.352) and OS ($p = 0.033$, HR = 2.011) (Fig. 2A, B). Five-year survival was achieved in 70.7% of patients

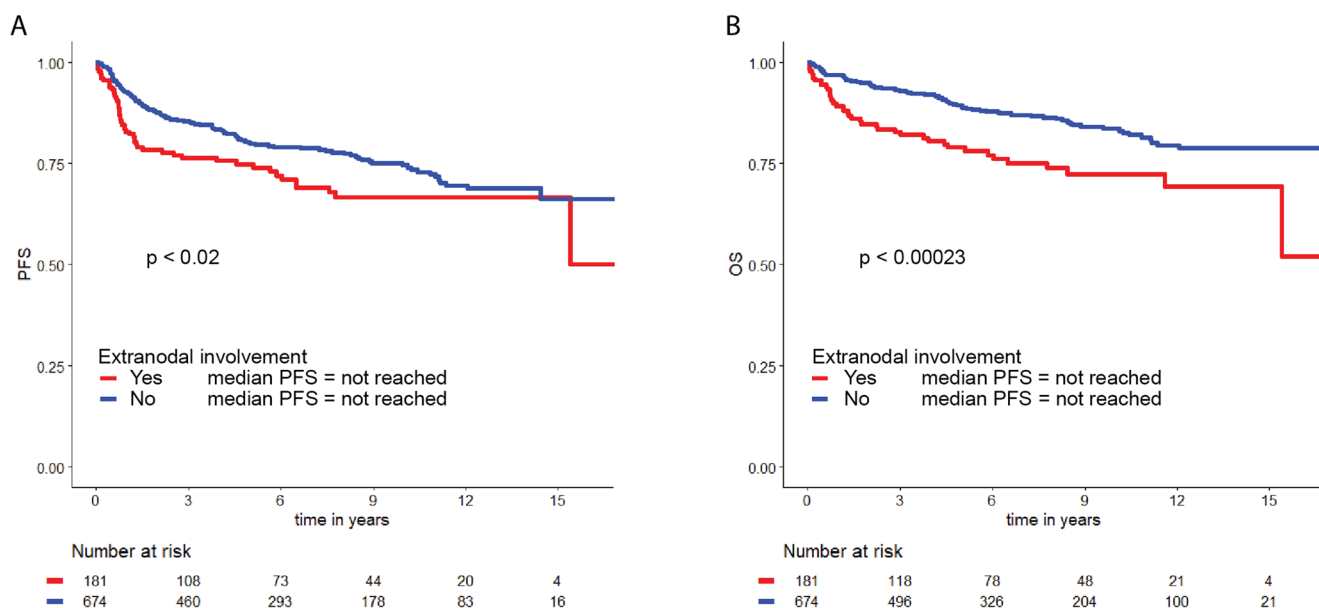


Fig. 1 Kaplan–Meier survival curves estimating PFS (A) and OS (B) in patients with HL according to extranodal manifestation of disease

(0.569–0.878; 95% CI), and 15-year survival was achieved in 56.7% of patients (0.406–0.792; 95% CI). Five-year PFS was achieved in 59.3% of patients (0.449–0.784; 95% CI), and 15-year PFS was achieved in 46.9% of patients (0.318–0.691; 95% CI).

An adverse trend in OS was also observed in the case of extranodal bone marrow involvement ($p=0.065$, HR=2.075). In contrast, a better prognosis was observed in patients in whom we observed localized involvement of an associated extralymphatic organ or site (PFS – $p=0.009$, HR=0.367; OS – $p=0.011$, HR=0.323) (Fig. 2C, D). Five-year survival was achieved in 89.8% of patients (0.815–0.988; 95% CI), and 15-year survival was achieved in 86.9% of patients (0.774–0.975; 95% CI). Five-year PFS was achieved in 86.4% of patients (0.774–0.964; 95% CI), and 15-year PFS was achieved in 83.4% of patients (0.733–0.949; 95% CI).

Extranodal involvement of other organs studied did not have a statistically significant effect on the prognosis of HL patients (Table 5). Similarly, multiple organ involvement did not impair OS or PFS compared with patients in whom extranodal involvement of only one organ was observed.

By applying the stepwise selection procedure on Cox model for OS, we identified the best linear combination of independent predictors, which minimizes Akaike information criteria. The best model consists of extranodal involvement, age at diagnosis, gender, and radiotherapy (Table 6).

4 Discussion

Our study provides new insights into the impact of extranodal involvement on the prognosis of patients with HL. The predominance of extranodal manifestations in patients in clinical stage IV, as demonstrated by our data, is consistent with staging for HL based on the Lugano classification, which is derived from the Ann Arbor staging system.

Our data also show that extralymphatic HL infiltration occurred most frequently in the lungs, followed by bone, liver, and chest wall. This observation is broadly consistent with data in the available literature, although some studies mention the liver as the most common site of dissemination [19, 20]. However, it is possible that preferential dissemination sites may vary across age groups. Specifically, Sharma et al. reported in their study that the most common site was the liver (23.07%), followed by bone (15.38%) and the lung (15.38%). Also of interest in this study is the number of extranodal diseases, which accounted for 50% of the total cases studied. This is more than twice as high compared to the 21% observed by us. However, this study was conducted on elderly Indian patients with a mean age of 65.9 years at diagnosis and a range of 60–80 years. The patients in our study were much younger with a median age at diagnosis of 37 years. In addition, the study discussed here followed only 13 patients with extranodal disease, a very small number for relevant statistical evaluation of the data [21]. Our study further confirmed that extranodal manifestation significantly worsens both PFS and OS in HL patients. This could correspond to the fact that extranodal involvement is one of the negative prognostic factors in early stages of HL and to the fact that extranodal involvement in our study was

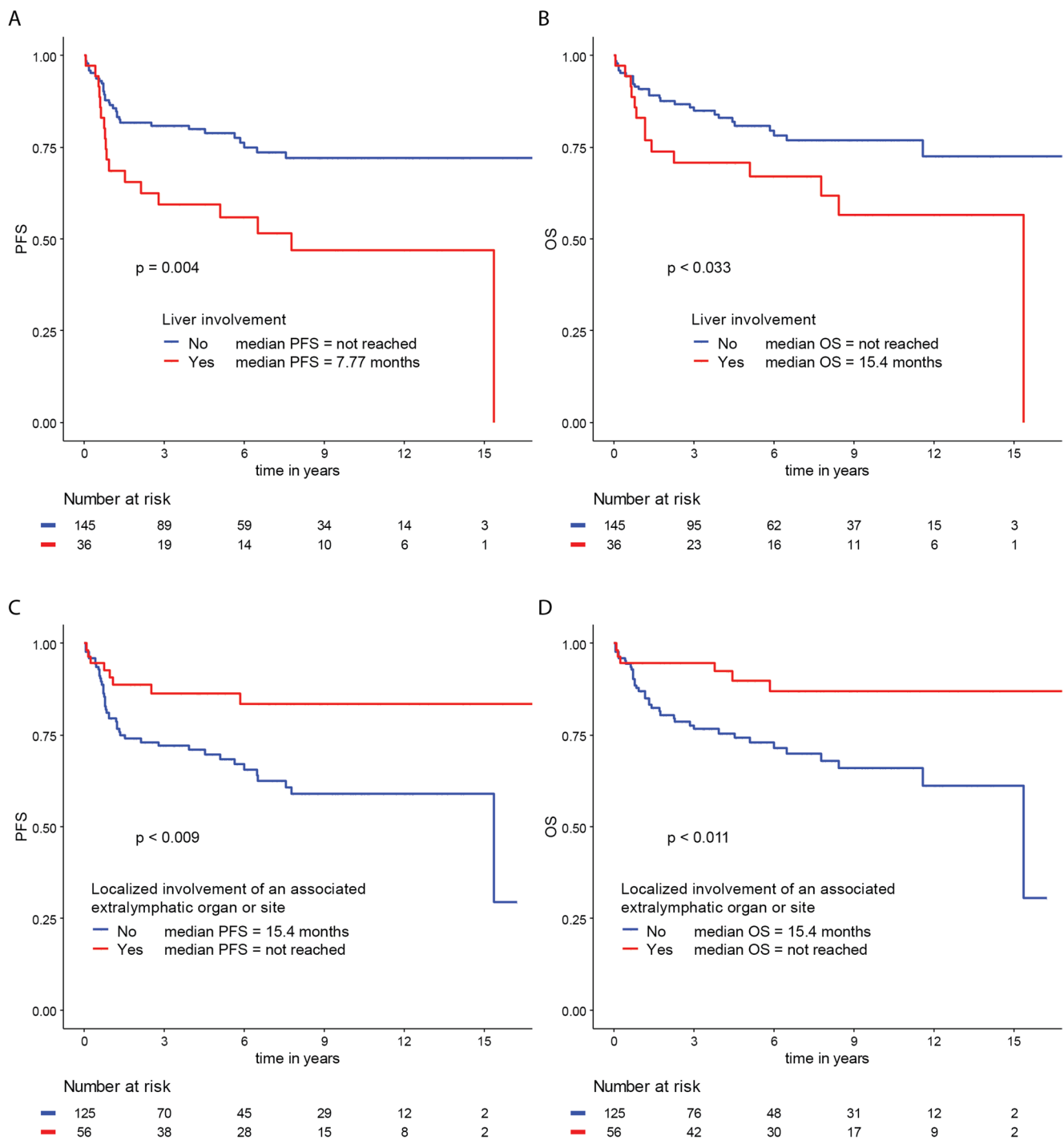


Fig. 2 Kaplan–Meier survival curves estimating PFS (**A**) and OS (**B**) in patients with HL according to extranodal manifestation in the liver; and PFS (**C**) and OS (**D**) according to localized involvement of an associated extralymphatic organ or site

predominantly observed in stage IV, which is itself associated with worse survival. According to the American Cancer Society, the five-year relative survival rates are 92% for localized HL and only 82% for more advanced HL that has reached distant organs such as the lungs or bone marrow. For all patients is the five-year relative survival rates 88%,

which corresponds with our consecutive cohort where this survival rate is 87.1% [6, 22, 23].

Interestingly, we observed a significantly worse prognosis in patients with extranodal liver involvement. To date, not many studies have been published addressing this phenomenon. However, an older paper from 1991 conducted on 56 patients with a diagnosis of Stage IV Hodgkin's disease

Table 5 Impact of extranodal involvement of different anatomical regions on the prognosis of patients with HL

Localization	Progression-free survival				Overall survival			
	HR	95% CI		p-value	HR	95% CI		p-value
*Localized Involvement	0.367	0.172	0.781	0.009	0.323	0.136	0.769	0.011
Lung	0.699	0.393	1.245	0.224	0.787	0.420	1.472	0.453
Pleura	0.000	0.000	Inf	0.997	0.000	0.000	Inf	0.997
Liver	2.352	1.324	4.179	0.004	2.011	1.058	3.823	0.033
Oesophagus	2.447	0.337	17.770	0.376	3.252	0.445	23.750	0.245
Kidneys	0.000	0.000	Inf	0.997	0.000	0.000	Inf	0.997
Skeleton	0.822	0.400	1.692	0.595	0.645	0.272	1.534	0.322
Bone marrow	1.635	0.766	3.489	0.204	2.075	0.957	4.500	0.065
Pericardium	1.682	0.232	12.190	0.607	1.853	0.254	13.500	0.543
Breast	0.000	0.000	Inf	0.997	0.000	0.000	Inf	0.997
Chest wall	0.538	0.229	1.262	0.154	0.553	0.217	1.409	0.214
Muscle	1.015	0.246	4.184	0.983	0.584	0.080	4.259	0.596
Pancreas	2.054	0.282	14.970	0.478	2.774	0.377	20.400	0.316
Thyroid gland	2.007	0.277	14.560	0.491	2.089	0.287	15.220	0.467
Other	0.621	0.151	2.555	0.509	0.809	0.195	3.355	0.770

*Localized involvement of an associated extralymphatic organ or site; **Inf** – Infinity

Table 6 Cox regression analysis of the effect of common Hodgkin's lymphoma prognostic factors on survival of HL patients

Evaluated parameter	Univariate Cox model				Multivariate Cox model			
	HR	95% CI	p-value	p-value (logrank)	HR	95% CI	p-value	Model p (logrank)
Extranodal manifestation (ref. No)								$<2*10^{-16}$
Yes	1.999	1.383	2.890	0.0002	1.460	0.967	2.203	0.0718
Clinical stage (ref. I)								
II	0.392	0.211	0.729	0.0031				$2*10^{-8}$
III	1.095	0.596	2.014	0.770				
IV	1.471	0.798	2.712	0.217				
Age at diagnosis	1.086	1.074	1.099	$<2*10^{-16}$	1.085	1.072	1.098	$<2*10^{-16}$
Sex (ref. Female)								
Male	1.681	1.17	2.416	0.004	1.503	1.037	2.177	0.0313
Radiotherapy (ref. Yes)								
No	2.733	1.856	4.024	$1*10^{-7}$	1.628	1.072	2.472	0.0222

involving the liver shows that 10-year survivals were 44%, and progression-free survival were 42% (median follow-up 81 months) [24]. This appears to be a worse prognosis in the context of another study from the same period, which, when analysing the effect of chemotherapy dose reductions on survival in patients with advanced Hodgkin's disease stage IIIB or IV treated by three double courses of C-MOPP/ABVD chemotherapy followed by either one further course or by involved-field radiotherapy, described a survival of 90% at 9 years of follow-up in group receiving full dose therapy, and 40% probability of survival at 6 years of follow-up in patients treated with reduced doses. However, this study included only 35 patients [25]. The poor prognosis of patients with liver involvement is also consistent with some case reports describing vanishing bile duct syndrome (VBDS) and idiopathic cholestasis (IC) in association with HL. They are rare HL-associated conditions that often lead to liver failure and death. In Ballonoff et al. statistical analysis, 1-year OS and liver failure-free survival (LFFS) were

43% and 41%, respectively, in thirty-seven cases of HL-related VBDS/IC (median follow-up was 7 months) [26].

On the other hand, bone marrow involvement, which in our study was also associated, although not statistically significant, with a worse prognosis in HL patients, has not been described in this context so far. There are studies, which have shown that the prognosis of HL patients with primary bone marrow involvement does not appear to be worse than that of other advanced-stage HL patients; and that the duration of complete remission and survival in HL patients with bone marrow involvement can be comparable to those without bone marrow involvement [27, 28]. However, both of these studies are very old and do not reflect the current management of patients with HL.

Conversely, local spread of HL to surrounding organs from lymph nodes represents a better prognosis, suggesting that direct local spread may be less indicative of systemic disease and more amenable to curative treatment modalities. Distant progression in HL, which involves the spread

of tumor to distant parts of the body like the lungs, liver, or bone marrow, has been associated with lower survival rates compared to localized or regional progression. The 5-year relative survival rates for HL based on the extent of spread are as follows: localized (93%), regional (95%), and distant (83%) [23].

Although univariate Cox regression analysis of the effect of common HL prognostic factors on patient survival confirmed extranodal manifestation as significant, multivariate analysis showed a stronger effect of clinical stage, age and gender of patients on survival. The effect of radiotherapy on prognosis was also observed. However, this observation is probably related to the fact that radiotherapy is most often indicated in patients in clinical stage I and II rather than to a biological effect.

Although local progression may not always predict a better prognosis compared to distant progression, understanding the specific sites and extent of disease spread is essential for tailoring treatment strategies and predicting patient outcomes in HL.

5 Conclusion

In conclusion, our study demonstrates a significant impact of extranodal involvement on survival outcomes in HL patients, with liver involvement being of particular prognostic importance. Overall, our observations point to the need for a more nuanced approach to prognosis and treatment planning with respect to specific sites of extranodal involvement. By further refining our knowledge of prognostic factors in HL, we can improve patient stratification and outcomes in this complex disease.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

Ethical Approval The study involving human participants was reviewed and approved by the Local ethics committee of University Hospital Brno, Brno, Czech Republic.

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7. Exprese PD-L1 u Hodgkinova lymfomu a její prognostický význam

Exprese ligandu programované buněčné smrti 1 (Programmed Death-Ligand 1, PD-L1) představuje u klasického Hodgkinova lymfomu (cHL) jeden z klíčových mechanismů nádorového imunitního úniku. Zvýšená exprese PD-L1 je u cHL podmíněna především genetickými alteracemi v oblasti 9p24.1, které vedou ke zvýšení počtu kopií genu CD274 a následně k jeho zvýšené expresi. Ke zvýšené expresi PD-L1 mohou přispívat také další mechanismy, včetně konstitutivní aktivace transkripčního faktoru AP-1 a u EBV-pozitivních případů signalizace zprostředkované virovým proteinem LMP1 (latent membrane protein 1).^{73,74}

Významným biologickým znakem nádorových Hodgkinových a Reedových–Sternbergových buněk (HRS) je velmi častá přítomnost genetických alterací v chromozomální oblasti 9p24.1. Tato oblast obsahuje geny CD274 (PD-L1) a PDCD1LG2 (PD-L2) a rovněž gen JAK2. Analýza pomocí fluorescenční in situ hybridizace (FISH) prokázala alterace lokusu 9p24.1 u 105 ze 108 (97 %) nově diagnostikovaných případů cHL, přičemž 5 % případů vykazovalo polysomii, 56 % zvýšení počtu kopií lokusu (copy gain) a 36 % jeho amplifikaci.¹⁸

Genetické změny v oblasti 9p24.1 zvyšují expresi PD-L1 a PD-L2 prostřednictvím zvýšení genové dávky a současně aktivací signální dráhy JAK/STAT v důsledku zvýšené aktivity JAK2, která dále podporuje transkripci CD274.^{18,73} U EBV-pozitivních případů cHL může ke zvýšené expresi PD-L1 přispívat rovněž virový protein LMP1 prostřednictvím aktivace transkripčního faktoru AP-1 a signální dráhy JAK/STAT. Tento mechanismus může vést k vysoké expresi PD-L1 i v případech bez výrazného zvýšení počtu kopií lokusu 9p24.1.⁷⁴

Za charakteristický biologický rys cHL lze považovat výrazný nepoměr mezi malým zastoupením maligních Hodgkinových a Reedových–Sternbergových buněk (HRS), které tvoří zpravidla méně než 5 % nádorové tkáně, a rozsáhlým nádorovým mikroprostředím, jež tvoří převážnou část nádorové masy. Toto mikroprostředí je tvořeno heterogenním infiltrátem, zejména T-lymfocyty, makrofágy, B-lymfocyty, eozinofily a dalšími buněčnými populacemi. Exprese PD-L1 a PD-L2 na HRS buňkách a PD-L1 na některých buňkách nádorového mikroprostředí, zejména makrofázích, přispívají k vytvoření imunosupresivního mikroprostředí. Vazba těchto ligandů na receptor PD-1 exprimovaný na T-lymfocytech aktivuje inhibiční signalizaci,

kteřá tlumí jejich aktivaci a efektorové funkce a při dlouhodobé stimulaci může přispívat k jejich funkčnímu vyčerpání a potlačení protinádorové imunitní odpovědi.^{18,67}

Z prognostického hlediska je významná zejména amplifikace lokusu 9p24.1. U pacientů léčených konvenčními léčebnými režimy byla vyšší míra alterací 9p24.1 spojena s vyšší expresí PD-L1 a PD-L2 a s nepříznivějšími klinickými charakteristikami. V analýze Roemera et al. byla amplifikace 9p24.1 častější u pacientů s pokročilým stadiem onemocnění a byla spojena s významně kratším přežitím bez progrese (PFS). V univariační analýze představovala amplifikace 9p24.1 významný prognostický faktor, zatímco v multivariační analýze její prognostický význam nedosáhl statistické významnosti.¹⁸ Je však vhodné zdůraznit, že prognostický význam jednotlivých typů alterací 9p24.1 není zcela jednoznačný a nelze jej interpretovat pouze jako přímý vztah mezi intenzitou exprese PD-L1 a klinickým průběhem onemocnění.

To, co představovalo v éře konvenční chemoterapie jeden z biologických mechanismů spojených s nepříznivým průběhem onemocnění, se v éře moderní imuno-onkologie stalo významným terapeutickým cílem. Biologická závislost cHL na signalizaci PD-1/PD-L1 přispívá k jeho mimořádné citlivosti k inhibitorům kontrolních bodů imunitní odpovědi. Monoklonální protilátky blokující receptor PD-1, zejména nivolumab a pembrolizumab, vedou u relabujícího a refrakterního cHL k vysokému podílu léčebných odpovědí a významně změnily léčebný přístup k tomuto onemocnění.^{67,75} Významný další posun představovalo zařazení inhibitorů PD-1 do prvoliniové léčby pokročilého cHL. Studie S1826 prokázala u nově diagnostikovaných pacientů s pokročilým cHL lepší výsledky léčby při kombinaci nivolumabu s AVD ve srovnání s brentuximabem vedotinem v kombinaci s AVD, čímž dále posílila význam osy PD-1/PD-L1 jako terapeutického cíle v primární léčbě cHL.²⁵

Přibližně u 15–20 % nemocných s cHL nedochází navzdory účinné primární léčbě k dosažení dlouhodobé remise. V následující studii jsme hodnotili prognostický význam exprese PD-L1 na Hodgkinových–Reedových–Sternbergových buňkách ve vztahu k riziku relapsu a primárně refrakternímu onemocnění. Retrospektivní analýza 120 nemocných s dlouhodobým mediánem sledování 90 měsíců prokázala významnou asociaci mezi pozitivitou PD-L1 a nepříznivým průběhem onemocnění. Zatímco ve skupině s negativní expresí PD-L1 nebyl během sledování zaznamenán žádný relaps ani refrakterní průběh, u nemocných s pozitivní expresí PD-L1 došlo k relapsu nebo rozvoji refrakterního onemocnění u 28 % pacientů. Studie tak přispěla k objasnění prognostického významu exprese PD-L1 u cHL a podpořila předpoklad, že PD-L1 může představovat potenciálně relevantní biomarker pro identifikaci nemocných s vyšším rizikem selhání primární léčby.

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Prognostic Significance of Immune-checkpoint Molecule PD-L1 in Classical Hodgkin Lymphoma: A Clinicopathologic Study of 120 Cases

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Abstract. *Background/Aim:* Classic Hodgkin lymphoma (cHL) is a common B-cell malignancy. Despite the good prognosis, in some patients the standard chemotherapy and radiotherapy-based approach does not lead to long-term remission, and these patients eventually relapse. Moreover, the primary refractory disease is of major concern regarding prognosis. *Patients and Methods:* We performed a retrospective analysis to evaluate PD-L1 expression in 120 patients with classic Hodgkin lymphoma (cHL). *Results:* The median follow-up of the entire group of patients was 90 months. After initial therapy, complete remission was achieved in 113 (94.2%) patients. During the follow-up, cHL relapse/refractory disease was reported in 23 (19.2%) cases. A total of five patients died during the follow-up period, all from cHL progression. When determining PD-L1 expression on Hodgkin-Reed-Sternberg (HRS) cells, 37 cases (30.8%) were evaluated as negative, and 83 cases (69.2%) as positive. In the negative PD-L1 group of patients, no cHL relapse/refractory disease was observed during the follow-

up period. However, out of 83 patients with positive PD-L1 expression on HRS cells, 23 (28%) showed relapse/refractory cHL. *Conclusion:* A significantly higher relapse rate was observed in PD-L1-positive patients diagnosed with cHL.

Classic Hodgkin lymphoma (cHL) is a common B-cell malignancy with increased incidence in young adults and those over 55 years of age (1, 2). Generally, cHL has a good prognosis; long-term remission is achieved in more than 80% of patients (3). Unfortunately, in some patients, the standard chemotherapy and radiotherapy-based approach does not lead to long-term remission, and these patients eventually relapse. Moreover, the primary refractory disease is of major concern regarding prognosis (4, 5).

Compared to other lymphomas, cHL contains only a small portion of malignant cells in the tumor – Hodgkin-Reed-Sternberg (HRS) cells account for only 1% - 5% of all cells (6). The tumor microenvironment (TME) mostly consists of inflammatory cells, including macrophages, CD4+ and CD8+ T cells, plasma cells, eosinophils, and other immune cells (7). However, antitumor immune response is limited. Furthermore, studies show that HRS cells produce molecules that limit the efficacy of T cell-mediated antitumor immune responses (6). Primary HRS cells express programmed cell death-1 ligand 1 (PD-L1), while tumor-infiltrating T cells express the coinhibitory receptor, programmed death-1 (PD-1) (7).

The function of PD-1 signaling is to abrogate T cell-mediated immune responses (8). Normal antigen-presenting cells, dendritic cells, and macrophages express PD-1 ligands that bind PD-1 receptors on activated T cells (8, 9). Then, PD-1 receptor recruits the Src homology 2 domain-containing protein tyrosine phosphatase-2 (SHP2) phosphatase to the

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Key Words: Classic Hodgkin lymphoma, PD-L1 expression, treatment, overall survival, relapse.



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immunoreceptor complex, resulting in attenuation of T cell receptor (TCR) signaling (8). PD-1 signaling results in “T-cell exhaustion”, temporary inhibition of activation and proliferation that can be reversed if the PD-1 signal is removed (2). Furthermore, PD-L1 promotes the induction and maintenance of PD-1+ T regulatory cells (10).

The PD-1 ligand genes, *PD-L1* and *PD-L2*, are located on chromosome 9p24.1 and are separated by 42 kilobases (8). Interestingly, a regulatory loop with Janus kinase 2 (JAK2), located upstream from *PD-L1* on 9p24.1, further augments PD-1 ligand expression in cHL (5).

PD-1 ligands are over-expressed and associated with an unfavorable prognosis in tumors, including malignant melanoma, colon, pancreatic, hepatocellular, and ovarian carcinomas (11–16). They are also associated with increased tumor invasiveness (17). In cHL, amplification of the *PD-L1* and *PD-L2* genes in HRS cells has been described (18). Subsequently, inhibition of PD-1 receptor binding to PD-L1 will potentiate the anti-tumor T-cell response and consequently reduce tumor growth (19) and thus may alter the current poor treatment outcomes in patients with relapsed/refractory cHL (20).

In our study, we analyzed the expression of PD-L1 on HRS cells and compared its level with treatment outcome of patients with cHL.

Patients and Methods

Clinical characteristics. Between 2003 and 2016, 713 individuals were diagnosed with cHL at the Department of Internal Medicine, Hematology and Oncology, University Hospital Brno, Czech Republic. Out of these, 120 patients were included into this retrospective analysis. Before entering the study, all patients signed the informed consent form approved by the Ethics committee of the hospital in accordance with the current version of the Helsinki Declaration.

The analyzed group of patients consisted of 52 (43.3%) men and 68 (56.7%) women treated and monitored by members of cHL group of our department. The median age at diagnosis was 30.5 years (range=14-76). Most patients were diagnosed at clinical stages I and II (78 patients, 65%), whereas 53 (35%) were diagnosed at stages III and IV. There were 85 cases of nodular sclerosis subtype (NSCHL), 27 cases of mixed cellularity subtype (MCCHL), 7 cases of lymphocyte-rich subtype (LRCHL), and 1 case of lymphocyte depleted subtype (LDCHL). The median follow-up period of our patients was 90 months (range=40-166 months). A total of five patients died during the follow-up of the group from cHL progression. All clinical characteristics are described in Table I.

Treatment protocols. Patients were treated with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) chemotherapy regimens; 71 (59.2%) of the patients underwent radiotherapy as part of the initial treatment. cHL patients in localized stage I and II without risk factors were treated with 2 cycles of ABVD and radiotherapy (20-30 Gy IF). Patients with localized clinical stage I and II and risk factors were treated by 4 cycles of ABVD or 2 cycles of BEACOPP and 2 cycles of ABVD.

Table I. *Clinical characteristics of classic Hodgkin lymphoma (cHL) patients (N=120).*

Sex	Men	52	43.3%
	Women	68	56.7%
Age at diagnosis	Median	30.5	years
	Minimum	14	years
	Maximum	76	years
HL type	NSCHL	85	70.8%
	MCCHL	27	22.5%
	LRCHL	7	5.8%
	LDCHL	1	0.8%
Stage	I	9	7.5%
	II	69	57.5%
	III	23	19.2%
	IV	19	15.8%
B symptoms	Yes	53	44.2%
	No	67	55.8%
Extranodal invasion	Yes	25	20.8%
	No	95	79.2%

NSCHL: Nodular sclerosis cHL; MCCHL: mixed cellularity cHL; LRCHL: lymphocyte-rich cHL; LDCHL: lymphocyte depleted cHL.

Table II. *Treatment response in classic Hodgkin lymphoma patients.*

Disease state three categories	Number (%)	Disease state two categories	Number (%)
No relapse	97 (80.8%)	No relapse	97 (80.8%)
Early relapse	10 (8.4%)	Relapse	23 (19.2%)
Late relapse	13 (10.8%)		

After chemotherapy, all patients were treated with radiotherapy (30 Gy IF). Risk factors were defined based on current risk criteria (21). Patients in advanced stages III and IV were treated with 6-8 cycles of BEACOPP. Radiotherapy (30 Gy IF) was used only in cases when vital residuum remained after chemotherapy.

Immunohistochemistry. An antibody to PD-L1 (clone 28-8, dilution 1:100, Abcam, Cambridge, UK) was used in the immunohistochemical analysis. Clone 28-8 specifically reacts with extracellular domain of huPD-L1. The antibody was diluted using Ventana Antibody Diluent (Roche, Basel, Switzerland). Formalin-fixed, paraffin-embedded 4 µm thick sections from all tissue blocks were cut. The staining was performed using VENTANA BenchMark ULTRA (Roche). The protocol was based on heat induced epitope retrieval (HIER) in cell conditioning 1 (CC1), efficient heating time was 72 min. Then, slices were incubated for 16 min with the primary antibody and the linker for 4 min. OptiView (Ventana Medical Systems, Tucson, AZ, USA) was used as detection kit. Following dehydration in a series of concentrated ethanol baths and clearing in xylene, the preparations were mounted in Pentax (Pentax Labs, Kankakee, IL, USA). The expression of PD-L1 was evaluated by counting percent of positive cells to all neoplastic cells. Pathological evaluation was performed using a Nikon Eclipse 55i microscope (Nikon, Tokyo, Japan) equipped with 4x/0.10, 10x/0.30,

Table III. *PD-L1 positivity in Hodgkin-Reed-Sternberg (HRS) cells.*

Value	Number (%)	Three categories	Number (%)	Two categories	Number (%)
0	37 (30.8%)	– Negative + Low positivity	37 (30.8%)	– Negative + Positive	37 (30.8%)
5	12 (10.0%)		50 (41.7%)		83 (69.2%)
10	11 (9.2%)				
20	8 (6.7%)				
30	15 (12.5%)	++ High positivity			
40	4 (3.3%)				
50	3 (2.5%)		33 (27.5%)		
60	7 (5.8%)				
70	10 (8.3%)				
80	6 (5.0%)				
90	7 (5.8%)				

Table IV. *PD-L1 positivity in surrounding cells.*

Value	Number (%)	Three categories	Number (%)	Two categories	Number (%)
0	16 (13.3%)	– Negative + Low positivity	16 (13.3%)	– Negative + Positive	16 (13.3%)
1	44 (36.7%)		102 (85.0%)		104 (86.7%)
5	11 (9.2%)				
10	26 (21.7%)				
20	14 (11.7%)	++ High positivity			
30	5 (4.2%)				
40	2 (1.7%)				
60	1 (0.8%)		2 (1.7%)		
70	1 (0.8%)				

20×/0.50, 40×/0.75 and 60×/0.85 objective lenses Positivity for PD-L1 was categorized into three and two groups according as follows: 0=“– negative” and 1–49=“+ slightly positive”, 50 or more=“++ strongly positive” ; or a rougher division into 0=“– negative” and 1 or more=“+ positive”.

Statistics. Standard descriptive statistics was applied in the analysis; absolute and relative frequencies for categorical variables and mean supplemented with median and min-max range for continuous variables. Statistical significance of differences was computed using Fisher exact test for categorical variables and Kruskal-Wallis test for continuous variables. Influence of PD-L1 positivity on disease status was analyzed using logistic regression and described using odds ratio, its 95% confidence interval and statistical significance. The level of statistical significance was set at $\alpha=0.05$, all hypotheses were evaluated as two-sided. Analysis was computed using SPSS 24.0.0.1 (IBM Corporation, Armonk, NY, USA).

Results

Treatment. Complete remission after initial therapy was achieved in 113 (94.2%) patients, six patients progressed, one patient achieved only partial remission. During the follow-up,

23 (19.2%) patients relapsed; early relapse/refractory disease was observed in 10 (8.4%) patients and late relapse in 13 (10.8%) patients. In the group of patients with late relapse (≥ 12 months), the median relapse-free survival (RFS) was 36 months (13-68) (Table II).

Immunohistochemistry. PD-L1 positivity was determined on HRS cells as well as on surrounding cells. When determining PD-L1 expression in HRS cells, a total of 37 cases (30.8%) were evaluated as negative and 83 (69.2%) evaluated as positive, of which 50 (41.7%) were slightly positive and 33 (27.5%) strongly positive (Table III). In surrounding cells, a total of 16 samples (13.3%) were assessed as PD-L1 negative, 104 (86.7%) as PD-L1 positive, of which 102 (85.0%) were slightly positive and 2 (1.7%) strongly positive (Table IV).

Correlation between PD-L1 status and relapse/progression. Analysis of PD-L1 expression in HRS cells indicated that out of the 120 cHL patients, 37 PD-L1 negative patients did not relapse during the follow-up period (100%). Furthermore, out of 83 PD-L1 positive patients, 60 patients did not relapse

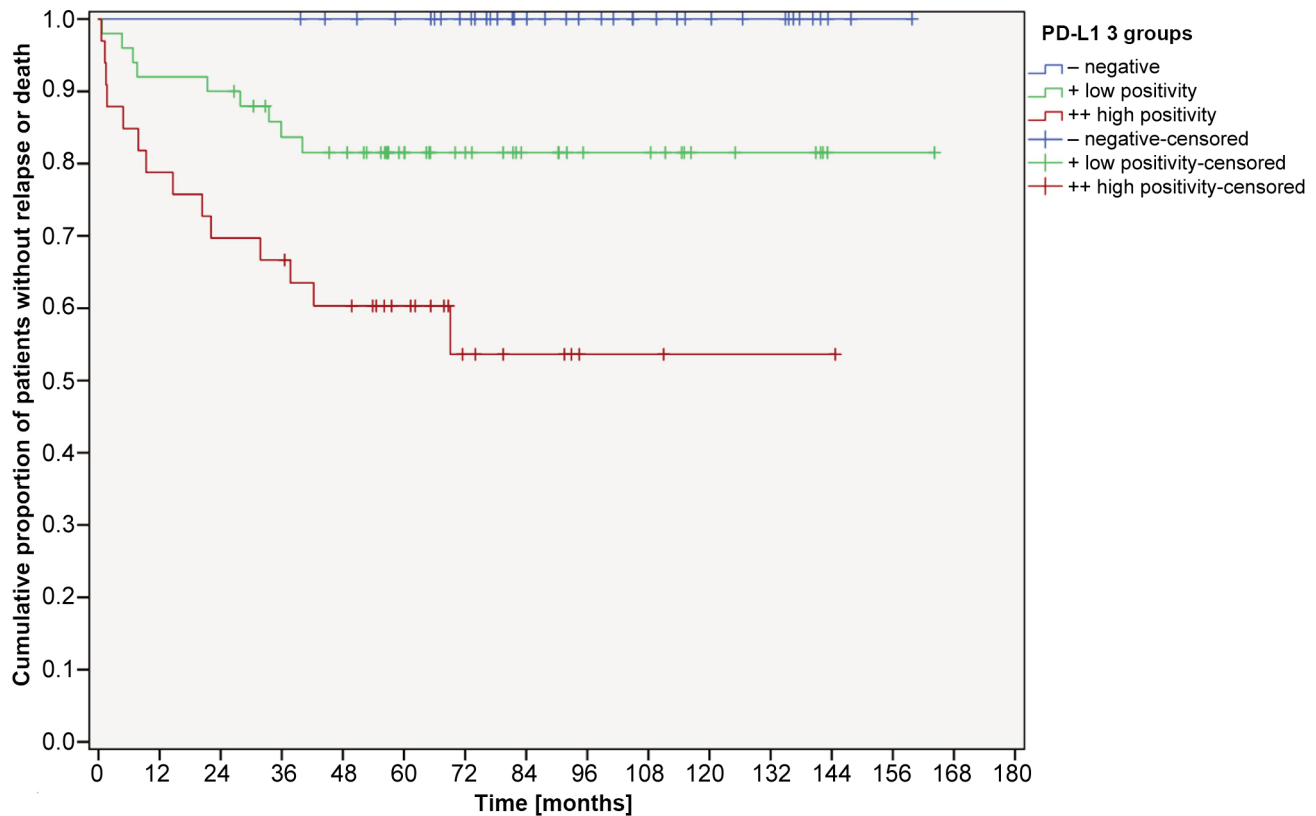


Figure 1. Relapse-free survival of classic Hodgkin lymphoma patients according to PD-L1 positivity in Hodgkin-Reed-Sternberg cells.

(72.3%) and 23 (27.7%) relapsed. Thus, a significantly higher relapse rate in patients with PD-L1 positive tumor cells was observed ($p<0.001$) (Figure 1).

Analysis of positivity of PD-L1 in surrounding cells indicated that there was no statistically significant difference between relapsed patients and patients without relapse (data not shown).

Furthermore, we divided the 83 PD-L1 positive patients into two groups based on PD-L1 expression: in the slightly positive (1%-50%) group, there were 50 patients; in the strongly positive group (51%-100%) there were 33 cases. We found that in the slightly positive group, 41 patients (82%) did not relapse, four (8%) relapsed early and five patients (10%) relapsed late. In the strongly positive group of patients, 19 patients (57.6%) did not relapse, six patients (18.2%) relapsed early and eight (24.2%) relapsed late ($p<0.001$) (Table V).

We did not find a statistically significant correlation with cHL clinical stage in the evaluation of PD-L1 positivity in HRS cells (Figure 1). On the contrary, a correlation was found between PD-L1 positivity in surrounding cells and the clinical stage of cHL. Increased value of positivity correlated with increased stage ($p=0.032$) (Figure 2).

Table V. PD-L1 positivity in Hodgkin-Reed-Sternberg cells and treatment outcome (N=120).

PD-L1	No relapse	Early relapse	Late relapse
-	37	0	0
(N=37; 30.8% patients)	(100.0%)		
+	41	4	5
(N=50; 41.7% patients)	(82.0%)	(8.0%)	(10.0%)
++	19	6	8
(N=33; 27.5% patients)	(57.6%)	(18.2%)	(24.2%)

Discussion

PD-1, also called CD279, was first identified in murine cell lines in 1992. PD-1 expression is induced in a variety of activated immune cells, such as macrophages, T cells, B cells, NKT cells and others. After PD-1 binds to its ligands (PD-L1 and PD-L2), the active immune cells are inhibited. In recent years, several studies have shown that tumor cells silence the immune system by expressing PD-L1. Thus, blockade of PD-1 and PD-L1 has been tested in ovarian, bladder, colorectal, and uterine cancers as well as Hodgkin lymphoma [reviewed

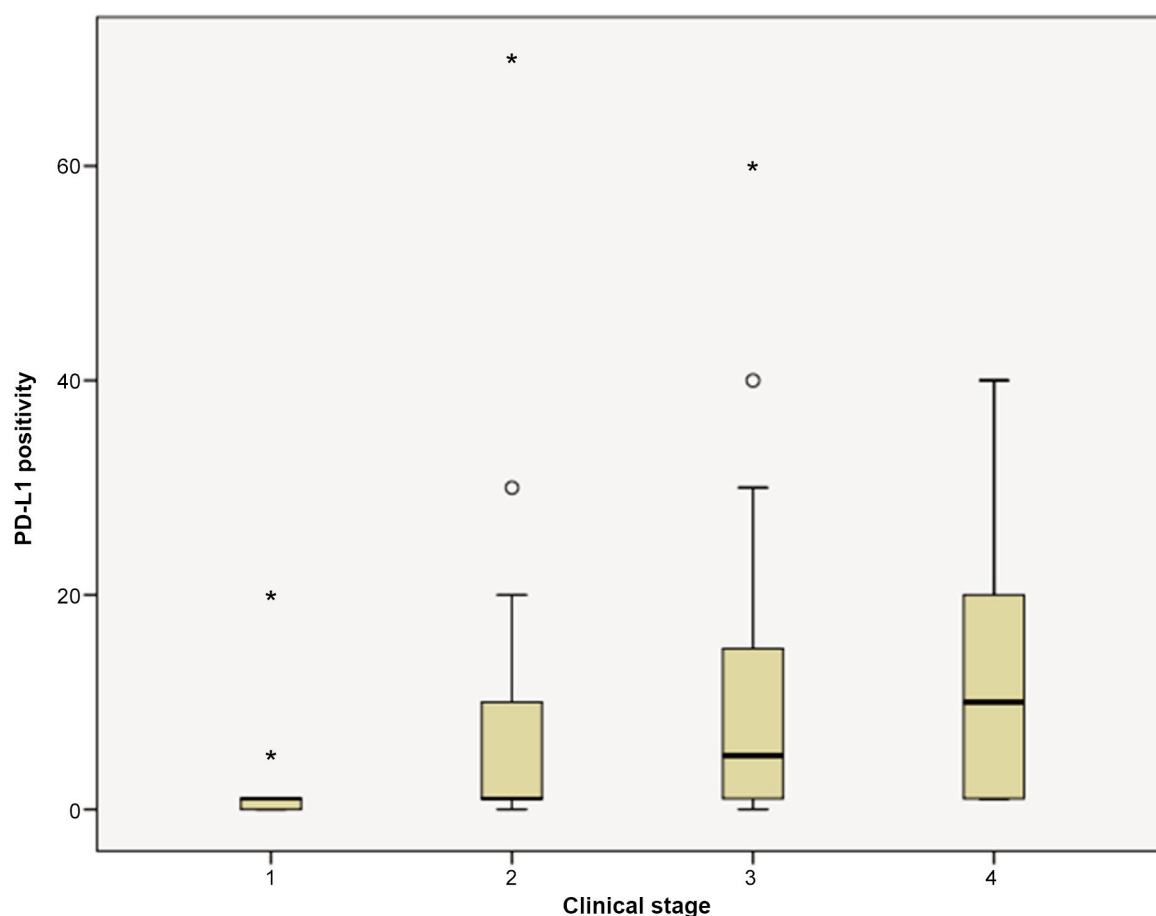


Figure 2. Relationship of PD-L1 positivity in background cells and stage of the disease ($p < 0.032$).

in (22)]. Nivolumab, a human IgG4 monoclonal antibody blocking PD-1 expression, was approved by the FDA in 2014 for the treatment of metastatic melanoma.

Despite recent indisputable success of cHL treatment, approximately 20% of patients do not achieve long-term remission and must be treated for relapse or refractory cHL. However, the efficacy of this treatment is lower; approximately 50% of patients with relapsed or refractory disease following first-line treatment can be cured by high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) and subsequent optional consolidation is performed in high-risk patients (23–29). In view of the new treatment options presented by PD-1 and PD-L1 inhibitors, many studies investigated the expression of PD-1/PD-L1 in cHL and its relevance to patients' prognosis.

PD-L1 over-expression in cHL is likely to be more common than in other types of lymphomas. The comparison between cHL primary mediastinal large B-cell lymphoma (PMBL), and gray zone lymphoma (GZL) demonstrated over-expression of PD-L1 ($\geq 70\%$ of tumor cells) in 62% of cHL, 15% of PMBL and 46% GZL cases (30).

In addition to the detection of PD-L1 expression in primary biopsies, the assessment of PD-L1 expression in relapsed or progressed cHL is clinically important. In the study of Vranic *et al.* (31), the expression of PD-L1 in 78 samples from patients with various treatment-resistant lymphomas was examined. The strongest and consistent expression (10/11 cases) was observed in cHL and PMBL (3/3). Diffuse large B-cell lymphomas (DLBCL) were often positive (13/26) regardless of sub-type. Follicular (1/8), peripheral T-lymphocytes (3/11) and mantle cells (1/8) were rarely positive in lymphomas, whereas small lymphoma lymphocytes/CLL and lymphomas in the peripheral zones were permanently negative (3/3) (31).

One study showed PD-1/PD-L1 expression on diagnostic samples of pediatric cHL patients at the time of diagnosis. This study included a group of patients in remission and a group of patients with relapsed/refractory cHL. Of the 42 patients analyzed, 31 achieved remission and the remaining 11 patients were classified as relapsing or refractory. At the time of diagnosis, low PD-1 expression was found in <20% of cases, while PD-L1 was expressed on tumor cells in all

cases; most cases showed a strong PD-L1 positivity ($\geq 50\%$). There were no significant differences in PD-1/PD-L1 expression levels between the groups (32).

The importance of PD-L1, PD-L2, and PD-1 expression in the prognosis of cHL patients was evaluated in a retrospective study involving a total of 109 cHL patients treated with ABVD. The median follow-up period was 4.91 years (range=0.17–17.33 years). Thirteen patients (11%) expressed PD-1 protein in the peritumoral microenvironment, which was associated with poor overall survival (OS). However, PD-L1 or PD-L2 expression level was not significant for OS. There was no correlation between PD-L1 and PD-1 expression or between PD-L2 and PD-1 expression. Multivariate analysis identified PD-1 protein as an independent prognostic factor for OS (33).

In another study, tissue samples of 87 cHL cases were analyzed. Co-expression of PD-1 and PD-L1 was found to be associated with shorter OS, although PD-1 or PD-L1 expression was not shown to be related to survival. In cases without PD-1 or PD-L1 expression, OS and disease-free survival (DFS) were 135 and 107 months, respectively. OS and DFS in cases expressing both PD-1 and PD-L1 were statistically significant at 24 and 20 months, respectively. Co-expression of PD-1 and PD-L1 was found to be an independent risk factor (34).

A study analyzing PD-L1/L2 genetic alterations in cHL evaluated a total of 108 biopsy samples from newly diagnosed cHL patients. It was shown that 97% of all evaluated cHL patients had identical changes in the PD-L1 and PD-L2 loci (5% polysomy, 56% copy number gain, 36% amplification). Progression-free survival (PFS) was significantly shorter in patients with 9p24.1 amplification, and the incidence of 9p24.1 amplification was higher in advanced stages of cHL (35).

It is also important to monitor the changes of PD-1 and PD-L1 expression before and during the treatment of cHL patients. In a group of 3 500 cHL patients, there were 11 patients with diagnostic cHL biopsy and a previous benign lymph node biopsy, which was later reclassified as cHL. These patients were marked as untreated. Thirty patients had a primary biopsy and a cHL relapse biopsy. These patients were described as treated. There was no statistically significant difference between biopsy 1 and 2 in untreated patients. In treated patients, a statistically significant increase in PD-1⁺ leukocytes, PD-L1⁺ leukocytes and PD-L1⁺ tumor cells was shown in cHL relapses (36).

In the CheckMate 205 study, the evaluation of the effect of the blockage of PD-1 receptor in patients with relapsed or refractory cHL who were treated with nivolumab was performed. Patients with higher 9p24.1 copies and over-expression of PD-L1 on HRS cells had better PFS. In HRS cells, expression of $\beta 2$ -microglobulin/MHC class I was not a significant predictive factor for complete remission or PFS on

nivolumab therapy. On the contrary, MHC class II expression on HRS cells was a significant predictive factor for complete remission. In patients with an interval >12 months between ASCT and nivolumab therapy, MHC class II HRS expression was associated with prolonged PFS (37). High prevalence of PD-L1 and PD-L2 expression has also been demonstrated in patients with cHL in the KEYNOTE study (38).

In conclusion, negative expression of PD-L1 correlated with RFS of cHL patients in concordance with previously published studies.

Conflicts of Interest

The Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contributions

ZK designed the study, analyzed clinical data, and wrote the manuscript. LK performed immunohistochemistry. JM obtained clinical data. JM performed statistical analysis. TA and ZK obtained clinical data. VK performed immunohistochemistry. All Authors read and approved the final manuscript.

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8. Pozdní následky léčby Hodgkinova lymfomu

Vzhledem k vysoké úspěšnosti léčby HL, kdy desetileté celkové přežití u mladších pacientů dosahuje přibližně 80–90 %, představuje problematika pozdní toxicity významnou součást dlouhodobé péče o vyléčené nemocné. Pozdní následky protinádorové léčby se mohou manifestovat s odstupem mnoha let až desetiletí od jejího ukončení a významně přispívají k dlouhodobé morbiditě a mortalitě pacientů vyléčených z HL. Riziko jejich vzniku závisí zejména na věku v době léčby, typu a kumulativní dávce použité systémové chemoterapie, rozsahu a dávce radioterapie a přítomnosti dalších rizikových faktorů, včetně kardiovaskulárních rizikových faktorů a kouření.^{76,77}

Sekundární malignity patří mezi nejzávažnější pozdní komplikace léčby HL a představují jednu z hlavních příčin pozdní mortality nesouvisející s relapsem či progresí HL. Jejich vznik je spojen jak s genotoxickým účinkem některých cytostatik, tak s karcinogenním účinkem ionizujícího záření. Terapií indukovaná akutní myeloidní leukémie (AML) a myelodysplastický syndrom (MDS) se typicky rozvíjejí v časnějším období po léčbě, zatímco zvýšené riziko vzniku sekundárních solidních nádorů přetrvává několik desítek let.^{6,78-86} Riziko vzniku terapií indukované AML/MDS souvisí zejména s expozicí alkylačním cytostatikům a etoposidu a je ovlivněno jejich kumulativní dávkou. Tyto sekundární hematologické malignity jsou často spojeny s nepříznivými cytogenetickými změnami a nepříznivou prognózou.^{78,81,85,86}

V rozsáhlé studii 3905 pacientů bylo riziko vzniku sekundární malignity ve srovnání s běžnou populací zvýšeno více než čtyřnásobně a zvýšené riziko přetrvávalo i více než 35 let po léčbě.⁶ Významná část těchto nádorů souvisí s předchozí radioterapií a vzniká v ozařovaném objemu nebo v jeho bezprostředním okolí. Karcinom prsu představuje jednu z nejvýznamnějších sekundárních malignit u žen, které v mladém věku, zejména před 30. rokem života a především v období puberty, podstoupily radioterapii hrudníku. Riziko jeho vzniku je ovlivněno zejména věkem při léčbě, dávkou záření, rozsahem ozářeného objemu a dobou od ukončení léčby.^{77,87-93} Významné je rovněž riziko karcinomu plic, přičemž mezi radioterapií hrudníku, expozicí alkylačním cytostatikům a kouřením existuje významná interakce, která riziko dále zvyšuje.⁹⁴⁻⁹⁹

Kardiovaskulární komplikace představují další významnou příčinu pozdní morbidity a mortality dlouhodobě přežívajících pacientů s HL. Na jejich vzniku se podílí především léčba antracykliny, zejména doxorubicinem, a radioterapie zahrnující oblast srdce a mediastina. Antracyklinová kardiotoxicita je závislá na kumulativní dávce a může vést k progresivnímu a potenciálně ireverzibilnímu poškození myokardu s následným rozvojem srdečního selhání.

Riziko kardiotoxicity se dále zvyšuje při současné expozici srdce radioterapii. Ozáření mediastina je spojeno s urychleným rozvojem koronární aterosklerózy a vyšším výskytem ischemické choroby srdeční, včetně infarktu myokardu. Pozdní kardiální komplikace mohou zahrnovat rovněž postižení srdečních chlopní, zejména jejich fibrózu a kalcifikaci, a poruchy převodního systému. Riziko těchto komplikací přetrvává po několik desetiletí po ukončení léčby a je ovlivněno zejména věkem pacienta v době léčby, dávkou záření a rozsahem ozářené oblasti.¹⁰⁰⁻¹⁰⁶

Pozdní plicní toxicita souvisí především s expozicí bleomycinu a radioterapií hrudníku. Bleomycin může vyvolat zánětlivé poškození plicního parenchymu s následným rozvojem intersticiálních změn a plicní fibrózy. Riziko plicní toxicity je ovlivněno mimo jiné kumulativní dávkou bleomycinu, věkem a dalšími faktory.^{107,108} Významnou součástí současných PET-adaptovaných léčebných strategií u pokročilého HL je proto možnost vynechání bleomycinu po dvou úvodních cyklech ABVD u pacientů s negativním interim PET/CT. Studie RATHL prokázala, že u pacientů s negativním PET/CT po dvou cyklech ABVD vedlo pokračování léčby režimem AVD bez bleomycinu k zachování účinnosti při současném snížení rizika plicní toxicity¹⁵

Mezi další sekundární malignity patří zejména nádory štítné žlázy, gastrointestinálního traktu a kožní nádory, jejichž zvýšený výskyt může souviset především s předchozí radioterapií a chemoterapií.^{6,77,109-112}

Z hlediska poruch endokrinních funkcí patří hypotyreóza mezi nejčastější pozdní následky radioterapie krční oblasti. Nejčastěji se rozvíjí během prvních několika let po léčbě, její riziko však přetrvává dlouhodobě a nové případy mohou být diagnostikovány i více než 20 let po ukončení léčby. Riziko jejího vzniku závisí především na dávce záření a objemu štítné žlázy vystaveném radioterapii. Manifestní hypotyreóza zpravidla vyžaduje dlouhodobou, často celoživotní substituční léčbu.^{113,114}

Gonadální toxicita je významně ovlivněna použitým chemoterapeutickým režimem,

kumulativní dávkou alkylačních cytostatik, věkem pacienta a u žen také výchozí ovariální rezervou. U mužů se může projevit přechodnou nebo trvalou poruchou spermatogeneze, v závažných případech až trvalou azoospermií. U žen může vysoká kumulativní expozice alkylačním cytostatikům vést ke snížení ovariální rezervy, poruše fertility a předčasné ovariální insuficienci s následnou předčasnou menopauzou. Riziko gonadálního poškození je výrazně vyšší při použití intenzivních režimů s vysokou expozicí alkylačním cytostatikům, zejména eskalovaného BEACOPP, než při léčbě režimem ABVD, který je z hlediska dlouhodobého ovlivnění fertility považován za méně rizikový. Riziko dále narůstá s počtem léčebných linií a při použití vysokodávkované chemoterapie následované ASCT. Vzhledem k možným dlouhodobým následkům by mělo být riziko poruchy fertility posouzeno již před zahájením léčby a u pacientů ve fertilním věku by měly být včas zváženy možnosti jejího zachování, zejména kryokonzervace spermatu u mužů a kryokonzervace oocytů nebo embryí, případně ovariální tkáně, u žen..¹¹⁵⁻¹²¹

Znalost spektra pozdních následků léčby vedla v posledních desetiletích k významným změnám v primární terapii HL. Patří mezi ně zejména redukce rozsahu radioterapie, postupný přechod od rozsáhlých ozařovaných polí k cílenějším konceptům IN-RT a IS-RT, snižování dávek záření a snaha o minimalizaci expozice cytostatikům spojeným s významnou dlouhodobou toxicitou. Součástí dlouhodobé péče o pacienty po úspěšné léčbě HL by měl být strukturovaný program sledování zaměřený na časnou detekci pozdních komplikací a redukci ovlivnitelných rizikových faktorů. U žen s významným rizikem sekundárního karcinomu prsu po předchozí radioterapii hrudníku je doporučován časný a intenzivnější screening prsů, zahrnující podle individuálního rizika mamografii a magnetickou rezonanci. Dále je nezbytné pravidelné hodnocení kardiovaskulárních rizikových faktorů, sledování funkce štítné žlázy a edukace pacientů zaměřená zejména na nekuřáctví, zdravý životní styl a prevenci dalších ovlivnitelných rizikových faktorů.

Následující retrospektivní studie hodnotila dlouhodobé riziko vzniku sekundárních malignit u souboru 871 pacientů s Hodgkinovým lymfomem s mediánem sledování 12 let. V průběhu sledování bylo diagnostikováno celkem 154 sekundárních malignit, přičemž jejich incidence byla ve srovnání s běžnou populací téměř trojnásobně vyšší (Standardized Incidence Ratio, SIR = 2,9). Nejvyšší relativní riziko (SIR) bylo zaznamenáno u karcinomu plic, karcinomu prsu a hematologických malignit. Sekundární malignity představovaly rovněž významnou příčinu pozdní mortality; v jejich důsledku zemřelo 71 pacientů, což odpovídalo 15 % všech úmrtí a 8 % celého sledovaného souboru. Analýza poukázala na význam předchozí protinádorové léčby, zejména radioterapie, pro rozvoj sekundárních malignit a prokázala rozdíly v jejich riziku v závislosti na lokalizaci ozařovaných polí. Nejvyšší AER (Absolute Excess Risk) sekundárních malignit vznikajících v ozařovaném poli bylo zaznamenáno u karcinomu prsu, kolorektálního karcinomu a karcinomu plic. Na základě získaných výsledků bylo navrženo individualizované schéma dlouhodobého sledování pacientů po léčbě Hodgkinova lymfomu, zohledňující pohlaví, charakter předchozí protinádorové léčby a zejména lokalizaci ozařovaných oblastí.

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ORIGINAL PAPER

Second cancers in Hodgkin's lymphoma long-term survivals: A 60-year single institutional experience with real-life cohort of 871 patients

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Summary

Background and Purpose: Appropriate surveillance guidelines for patients after successful treatment of Hodgkin's lymphoma (HL) are needed to reduce mortality of iatrogenic secondary cancers (SC). This large single institutional retrospective study analyses the risk of SC in HL patients treated outside of clinical trials over past decades.

Material and Methods: Consecutive series of HL patients were analysed with median follow-up 12 years. Standardised incidence ratio (SIR) and absolute excess risk (AER) were calculated for site-specific risk of SC.

Results: In total of 871 patients (491 men; median age 34 years), chemotherapy alone, radiotherapy alone, and combined treatment underwent 36%, 40%, and 24% patients. 154 SC were found with significantly increased SIR = 2.9 and AER = 80.8 for all cancers except of nonmelanoma-skin cancer. SC-related death occurred in 71 patients (15% of those who died, 8% of whole cohort). The most common SC were lung (17.5% of all malignancies, SIR = 3.2), breast carcinoma (15.6%, SIR = 4.4), and haematological malignancy (non-Hodgkin's lymphoma SIR = 13.1; leukaemia SIR = 5.8). For SC within radiation field, the highest AER was in breast (AER = 46.9), colorectal (AER = 22.8), and lung cancer (AER = 17).

Conclusions: Patients with HL are generally at great risk of developing SC, which is significantly increased especially by the use of radiotherapy. We suggested special follow-up schema for patients after initial HL treatment suitable for daily real-world clinical practice. The system depends on gender, form of HL treatment and especially the form of radiation therapy in terms of location of radiation fields.

1 | INTRODUCTION

Significant advances in the treatment of Hodgkin's lymphoma (HL) have been made over past decades, leading to HL, a very common cancers diagnosed in young adults, being one of the most curable cancers with high response rate to both chemotherapy and radiotherapy. With current standards of care, the 5-year and 10-year survival rates for HL are 86% and 80% of all stages, respectively.¹

Nevertheless, prolonged survival following successful HL treatment has been accompanied by several late sequelae affecting patients' quality of life and life expectancy, notably by second cancers (SC) since this late adverse effect contribute most to the substantial excess mortality after HL treatment. As a consequence, excess mortality >15 years after successful treatment of HL may be due to adverse side effects rather than HL itself, especially in patients with clinical stages I and II.^{2,3} Appropriate surveillance guidelines for HL survivors are needed to reduce mortality of this iatrogenic SC,⁴ especially with continuing efforts and achievements in the upfront treatment of HL patients including advances in immunotherapy.⁵

Real-world evidence research is an increasingly important supplement to basic and clinical research. Data about real-world patient experience treated outside controlled clinical trials may identify hidden gaps and biases of care which is provided within the frame of clinical trial. Thus, it may help to address all patients' needs in the primary treatment as well as in follow-up within daily clinical practice.

The aim of presented single institutional retrospective study was to analyse outcomes of patients treated for HL over past decades with respect to the risk of SC and to offer an appropriate follow-up surveillance recommendation suitable for real-world clinical practice.

2 | MATERIALS AND METHODS

2.1 | Patients

Consecutive series of patients treated for HL at Masaryk Memorial Cancer Institute between 1953 and 1996 were used in this retrospective analysis. Patients have undergone primary treatment that was standard of care at that time, all patients were treated outside of clinical trials. Data were collected in anonymised form from the electronic and written medical records which were acquired during the course of diagnosis, treatment and follow-up surveillance. Median follow-up was 12 years. Follow-up was considered starting from the date of HL diagnosis to the date of last reported vital status or death

What's known

- The increasing prevalence of cancer survivals is becoming a major healthcare issue related to cost-effective surveillance of these patients.
- Majority of patients with Hodgkin's lymphoma are cured and they carry a high risk of development of iatrogenic secondary cancers

What's new

- We described the patterns of secondary cancers depending on the provided treatment, especially in relation to irradiated parts of the body. This is one of the largest study with long follow-up of unselected consecutive cohort of patients treated outside of clinical trials and, thus, appeals to general clinical practice.
- We suggested special follow-up schema for patients after initial Hodgkin's lymphoma treatment suitable for daily real-world clinical practice

from any cause. Cancer cases diagnosed within 2 months after HL diagnosis were excluded.

2.2 | Statistical analysis

Standardised incidence ratio (SIR) is an estimate of the occurrence of cancer in a study population relative to what might be expected in the normal population. It is calculated by dividing the observed number of cancer cases (second and subsequent malignancies after the primary disease of HL) by expected number of cases. These were obtained by dividing cohort of patients into years by sex, age (5-year age groups), and period and by subsequent multiplication by pertinent sex-, age-, and period-specific cancer incidence rates estimated from the Czech National Cancer Registry (rates before 1977 were assumed equal to those observed in 1977-1979). For example a SIR of 1.7 is interpreted as 70% more cancer cases occurred than the expected number. 95% confidence intervals (CI) for SIR were derived assuming Poisson distribution of the observed number of cases. For SIR estimation of cancer cases occurring in the treatment field of initial radiotherapy, person-years in patients initially treated with noted radiotherapy regimen involving irradiation of the particular organ were counted.

Absolute excess risk (AER) is considered one of the best risk measures to express burden of disease. It was calculated by subtracting the expected number of cancer cases from the observed ones and by dividing the difference by the sum of the person-years. AER is reported per 10 000 person-years (PYR). For example, if absolute risk of developing cancer in 10 000 irradiated PYR is 100 cases (some cases as a consequence of irradiation, some cases as a spontaneous occurrence) and in 10 000 nonirradiated PYR is absolute risk 20 cases, than AER is 80 cases in 10 000 PYR. For male cancers (prostate and testicular) and female cancers (breast, uterine, and ovarian), only PYR accumulated by the patients of the respective sex were taken into account (6465 PYR for male and 6025 PYR for female cancers).

Cumulative incidence of the second malignancies was estimated considering competing risk of death. Cumulative incidence is calculated by the number of new cases during a period divided by the number of subjects at risk in the population at the beginning of the follow-up.

Statistical analysis was performed by package Stata/IC 10.1 [StataCorp]. Significantly different means there is less than 5% chance that the observed difference is the result of random fluctuation in the number of observed cancer cases. Site-specific risk of second cancer was performed separately according to (1) years after HL diagnosis, (2) type of initial therapy, and (3) presence within an irradiated field.

3 | RESULTS

3.1 | Basic characteristics

A total of 895 HL patients were treated between 1953 and 1996. From this group, 24 were excluded: 18 were lost from follow-up, two for inconsistent records, two had no treatment, two had history of other malignancy before HL, or less than 2 months after treatment of HL. Thus, 871 patients (491 men and 380 women; median age 34 years) were subjects of statistical analysis. Basic patients' characteristics are summarised in Table 1. Various histological subtypes

TABLE 1 Baseline characteristics of the cohort of Hodgkin's lymphoma patients

	Initial treatment			
Characteristic	CHT n = 314 (36.1%)	RT n = 349 (40.1%)	CHT+RT n = 208 (23.9%)	Total n = 871
Period				
<1980	89 (27.5%)	183 (56.5%)	52 (16.0%)	324
1980-1989	146 (37.2%)	148 (37.8%)	98 (25.0%)	392
1990-1999	79 (51.0%)	18 (11.6%)	58 (37.4%)	155
Sex				
Men	186 (37.9%)	192 (39.1%)	113 (23.0%)	491
Women	128 (33.7%)	157 (41.3%)	95 (25.0%)	380
Age				
<15	1 (3.1%)	23 (71.9%)	8 (25.0%)	32
15-24	74 (33.9%)	82 (37.6%)	62 (28.4%)	218
25-34	73 (35.4%)	82 (39.8%)	51 (24.8%)	206
35-44	50 (35.2%)	56 (39.4%)	36 (25.4%)	142
45-54	43 (39.4%)	42 (38.5%)	24 (22.0%)	109
55-64	37 (42.0%)	34 (38.6%)	17 (19.3%)	88
65+	36 (47.4%)	30 (39.5%)	10 (13.2%)	76
Stage of HL				
IA	5 (4.7%)	93 (87.7%)	8 (7.5%)	106
IB	0 (0.0%)	11 (84.6%)	2 (15.4%)	13
IIA	20 (10.3%)	135 (69.2%)	40 (20.5%)	195
IIB	18 (19.8%)	50 (54.9%)	23 (25.3%)	91
IIIA	40 (41.2%)	26 (26.8%)	31 (32.0%)	97
IIIB	61 (60.4%)	12 (11.9%)	28 (27.7%)	101
IVA	54 (68.4%)	6 (7.6%)	19 (24.1%)	79
IVB	112 (67.9%)	4 (2.4%)	49 (29.7%)	165
X	4 (16.7%)	12 (50.0%)	8 (33.3%)	24

HL, Hodgkin's lymphoma; CHT, chemotherapy; RT, radiotherapy.

of HL were as follow: 38% mixed cellularity, 25% nodular sclerosis, 14% lymphocyte predominant, 9% lymphocytic depletion, 14% not otherwise specified.

Three hundred and fourteen patients (314/871, 36%) underwent chemotherapy alone, 349 patients (349/871, 40%) radiotherapy alone, and the rest (208/871, 24%) underwent combined treatment by chemotherapy and radiotherapy. During the follow-up, 469 patients (469/871, 54%) died with 316 patients dying because of HL (316/469, 67%; 316/all 871, 36%). Second malignancy-related death occurred in 71 patients (71/469, 15%; 71/all 871, 8%). Reason of death in the rest of patients was mainly cardiovascular disease (23 patients) and infectious diseases (19 patients).

3.2 | Site-specific risk of second cancer

A total of 154 SC were found in the study population with significantly increased SIR = 2.9 (95% CI 2.5-3.4) and AER = 80.8 for all

cancers except of nonmelanoma skin cancer (NMSC). The most common SC were lung in 27 patients (27/154, 17.5% of all malignancies, SIR = 3.2; 95% CI 2.1-4.7) and breast carcinoma (24/154, 15.6%, SIR = 4.4; 95% CI 2.8-6.6). A significantly higher incidence was observed also in haematological malignancy as is non-Hodgkin's lymphoma (HNL) (SIR = 13.1; 95% CI 7.3-21.6) or leukaemia (SIR = 5.8, 95% CI 2.3-12.0). The incidence as well as SIR for other SC is listed in Table 2.

In the group of the most frequent SC found in our cohort, patients had the greatest AER of developing breast (AER = 30.8), followed by lung cancer (AER = 14.9), NHL (AER = 11.1) and leukaemia (AER = 4.6).

3.3 | Site-specific cumulative incidence of second primary malignancy after 5, 15, and 25 years

The cumulative incidence of SC after 5, 15, and 25 years after diagnosis of HL is summarised in Table S1. The cumulative incidence of all malignancies (outside NMSC) after 5 years is 2.0%, after 15 years 7.3%, and after 25 years 13.7%. In the next 25 years after initial treatment of HL, the risk is mainly in the development of breast cancer with the cumulative incidence of 3.3% (95% CI 1.7%-5.9%) and lung cancer 3.1% (95% CI 2.0%-4.5%).

3.4 | Site-specific risk of second cancer according to years after Hodgkin's lymphoma diagnosis

The increased risk of SC was observed in all time periods (SIR up to 5 years = 1.8, 95% CI 1.0-2.9; SIR 5-15 years = 2.7, 95% CI 2.0-3.5; SIR 15-25 years = 3.0, 95% CI 2.2-4.0; SIR >25 years = 4.2, 95% CI 3.1-5.7). In the first period, the most malignancies with greatest risk are haematological malignancies (SIR for NHL = 5.25, 95% CI 8.3-59.5 and SIR for leukaemia = 8.4, 95% CI 1.0-30.2), whereas in the last period, the most risky are thyroid (SIR = 14.7, 95% CI 1.8-52.9) and breast cancer (SIR = 10.6, 95% CI 5.6-18.1). The other SC are summarised in Table 3.

3.5 | Site-specific SIR of second cancer according to initial therapy

The risk of developing SC in relation to treatment modality used is summarised in Table 4. The highest risk of SC was in patients after radiotherapy, 96 SC in total (SIR = 4.0, 95% CI 3.3-4.9; the highest SIR for thyroid and breast cancer), however, a smaller but still significantly increased incidence was in patients who underwent combination of chemotherapy and radiotherapy (19 SC, SIR = 2.1, 95% CI 1.2-3.2; the highest SIR for HNL and leukaemia), or chemotherapy alone (39 SC, SIR = 1.9, 95% CI 1.4-2.7; the highest SIR for NHL and thyroid cancer). Cumulative incidence of the most common SC after radiotherapy is shown in Figure S1.

TABLE 2 Site-specific risk of SC after HL

Second malignancy	No. n = 154	SIR	95% CI	AER
NHL ^a	15	13.1 ^a	7.3-21.6	11.1
Thyroid ^a	8	11.9 ^a	5.1-23.4	5.9
Leukaemia ^a	7	5.8 ^a	2.3-12.0	4.6
Stomach ^a	10	4.4 ^a	2.1-8.1	6.2
Breast, females ^a	24	4.4 ^a	2.8-6.6	30.8
Liver	3	3.5	0.7-10.2	1.7
Melanoma of skin ^a	6	3.5 ^a	1.3-7.7	3.4
Soft tissue	1	3.3	0.1-18.3	0.6
Lung ^a	27	3.2 ^a	2.1-4.7	14.9
Kidney ^a	7	2.7 ^a	1.1-5.6	3.5
Colon and rectum ^a	19	2.5 ^a	1.5-3.9	9.2
Cervix uteri	4	2.5	0.7-6.3	4.0
Bladder	5	2.3	0.8-5.4	2.3
Oral cavity, pharynx	3	2.0	0.4-5.7	1.2
NMSC ^a	23	1.9 ^a	1.2-2.9	8.8
Ovary	2	1.5	0.2-5.6	1.2
Pancreas	2	1.2	0.1-4.3	0.2
Larynx	1	1.2	0.0-6.6	0.1
Corpus uteri	2	1.2	0.1-4.2	0.4
Biliary tract	1	1.1	0.0-6.4	0.1
Other cancers	2	0.7	0.1-2.6	-0.6
In situ neoplasms	2	0.7	0.1-2.4	-0.8
All cancers, except NMSC ^a	154	2.9	2.5-3.4	80.8

SC, second cancer; HL, Hodgkin's lymphoma; No., Number of cases; NHL, non-Hodgkin's lymphoma; NMSC, nonmelanoma skin cancer; SIR, standardised incidence ratio; CI, confidence interval; AER, absolute excess risk per 10 000 person-years.

^aIndicates significant result (CI not overlapping 1).

TABLE 3 Site-specific SIR of second primary malignancy according to years after Hodgkin lymphoma diagnosis

Second malignancy	0-5 years after HL		5-15 years after HL		15-25 years after HL		25 + years after HL	
	No.	SIR (95% CI)	No.	SIR (95% CI)	No.	SIR (95% CI)	No.	SIR (95% CI)
Thyroid ^a	0	0.0 (0.0-40.8)	2	9.1 ^a (1.1-32.9)	4	17.7 ^a (4.8-45.3)	2	14.7 ^a (1.8-52.9)
Breast, females ^a	1	1.4 (0.0-7.8)	5	3.0 ^a (1.0-7.0)	5	2.7 (0.9-6.4)	13	10.6 ^a (5.6-18.1)
Cervix uteri ^a	0	0.0 (0.0-11.2)	1	1.6 (0.0-8.8)	1	2.2 (0.1-12.0)	2	10.5 ^a (1.3-38.0)
Melanoma of skin ^a	0	0.0 (0.0-14.7)	2	3.4 (0.4-12.4)	1	1.8 (0.0-10.2)	3	9.3 ^a (1.9-27.3)
Uncertain behaviour ^a	1	12.6 (0.3-70.3)	0	0.0 (0.0-13.1)	1	3.1 (0.1-17.1)	2	9.0 ^a (1.1-32.4)
Kidney ^a	0	0.0 (0.0-10.0)	2	2.3 (0.3-8.3)	1	1.2 (0.0-6.9)	4	7.5 ^a (2.0-19.1)
Liver	0	0.0 (0.0-23.1)	2	6.6 (0.8-24.0)	0	0.0 (0.0-15.5)	1	6.3 (0.2-35.2)
Biliary tract	0	0.0 (0.0-21.8)	0	0.0 (0.0-12.2)	0	0.0 (0.0-15.6)	1	6.1 (0.2-33.7)
Colon and rectum ^a	1	0.8 (0.0-4.4)	6	2.3 (0.8-5.0)	5	2.3 (0.7-5.3)	7	4.7 ^a (1.9-9.7)
Oral cavity, pharynx	1	3.7 (0.1-20.4)	0	0.0 (0.0-7.0)	1	2.2 (0.1-12.2)	1	3.7 (0.1-20.5)
Prostate	2	4.7 (0.6-16.9)	0	0.0 (0.0-3.2)	0	0.0 (0.0-3.3)	3	3.6 (0.7-10.4)
NMSC ^a	1	0.6 (0.0-3.4)	4	1.0 (0.3-2.6)	9	2.4 ^a (1.1-4.5)	9	3.3 ^a (1.5-6.3)
Stomach ^a	0	0.0 (0.0-6.2)	4	4.8 ^a (1.3-12.3)	5	9.5 ^a (3.1-22.2)	1	3.2 (0.1-17.9)
Bladder ^a	0	0.0 (0.0-10.8)	1	1.4 (0.0-7.5)	3	4.7 ^a (1.0-13.9)	1	2.3 (0.1-12.8)
In situ neoplasms	0	0.0 (0.0-10.5)	1	0.9 (0.0-5.0)	0	0.0 (0.0-3.7)	1	2.1 (0.1-11.6)
Other cancers	0	0.0 (0.0-6.9)	0	0.0 (0.0-3.8)	1	1.3 (0.0-7.1)	1	2.0 (0.1-11.2)
Lung ^a	4	2.1 (0.6-5.4)	14	4.6 ^a (2.5-7.7)	7	3.3 ^a (1.3-6.7)	2	1.5 (0.2-5.3)
Oesophagus	0	0.0 (0.0-41.7)	0	0.0 (0.0-19.4)	0	0.0 (0.0-21.9)	0	0.0 (0.0-34.7)
Pancreas	0	0.0 (0.0-12.2)	0	0.0 (0.0-6.4)	2	4.1 (0.5-14.9)	0	0.0 (0.0-11.1)
Larynx	0	0.0 (0.0-19.5)	1	3.3 (0.1-18.1)	0	0.0 (0.0-16.6)	0	0.0 (0.0-29.1)
Soft tissue	0	0.0 (0.0-56.1)	0	0.0 (0.0-32.5)	1	12.2 (0.3-68.1)	0	0.0 (0.0-83.6)
Corpus uteri	1	3.8 (0.1-21.3)	1	1.9 (0.0-10.5)	0	0.0 (0.0-6.8)	0	0.0 (0.0-9.1)
Ovary	0	0.0 (0.0-17.4)	2	4.6 (0.6-16.8)	0	0.0 (0.0-9.2)	0	0.0 (0.0-14.8)
Testis	0	0.0 (0.0-27.9)	0	0.0 (0.0-16.0)	0	0.0 (0.0-30.3)	0	0.0 (0.0-120.8)
Brain, spinal cord	0	0.0 (0.0-22.1)	0	0.0 (0.0-11.7)	0	0.0 (0.0-14.6)	0	0.0 (0.0-25.7)
HL	0	0.0 (0.0-30.5)	0	0.0 (0.0-23.4)	0	0.0 (0.0-48.9)	0	0.0 (0.0-133.7)
NHL ^a	5	25.5 ^a (8.3-59.5)	4	10.1 ^a (2.8-25.9)	6	17.7 ^a (6.5-38.4)	0	0.0 (0.0-17.1)
MM	0	0.0 (0.0-46.8)	0	0.0 (0.0-24.3)	0	0.0 (0.0-28.7)	0	0.0 (0.0-41.8)
Leukaemia ^a	2	8.4 ^a (1.0-30.2)	2	4.7 (0.6-16.9)	3	9.1 ^a (1.9-26.6)	0	0.0 (0.0-17.9)
All cancers except NMSC	17	1.8 ^a (1.0-2.9)	49	2.7 ^a (2.0-3.5)	46	3.0 ^a (2.2-4.0)	42	4.2 ^a (3.1-5.7)

NMSC, non-melanoma skin cancer; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; MM, multiple myeloma; No., number of cases; SIR, standardised incidence ratio; CI, confidence interval.

^aIndicates significant result (CI not overlapping 1).

3.6 | Site-specific risk of second malignancy according to the irradiation field

Considering local nature of radiotherapy treatment, only potential SC within radiotherapy field was taken into account. For example, risk of secondary breast cancer was evaluated only in patients after mantle field irradiation or after radiotherapy of mediastinum or adjacent tissues. The highest risk was in developing NMSC (SIR = 15.5, 95% CI 3.2-45.4) and thyroid cancer (SIR = 14.1, 95% CI 5.2-30.8). The other SC are summarised in Table 5. Among the most frequent

second cancers within irradiated field in terms of AER were breast cancer (AER = 46.9), colon and rectal cancer (AER = 22.8), and lung cancer (AER = 17), except of NMSC.

4 | DISCUSSION

The risk of secondary cancer after successful initial treatment of HL was evaluated in this large retrospective single institutional study enrolling 871 patients from real-world practice since 1953. We

TABLE 4 Site-specific SIR of second primary malignancy, stratified according to initial therapy (CHT, RT, CHT+RT)

Second malignancy	RT		RT + CHT		CHT	
	No.	SIR (95% CI)	No.	SIR (95% CI)	No.	SIR (95% CI)
Oral cavity, pharynx	2	3.0 (0.4-10.7)	0	0.0 (0.0-13.0)	1	1.7 (0.0-9.7)
Oesophagus	0	0.0 (0.0-16.0)	0	0.0 (0.0-35.7)	0	0.0 (0.0-16.7)
Stomach ^a	6	5.8 ^a (2.1-12.7)	1	2.8 (0.1-15.6)	3	3.4 (0.7-10.0)
Colon and rectum ^a	13	4.0 ^a (2.1-6.8)	3	2.3 (0.5-6.9)	3	1.0 (0.2-2.9)
Liver	2	5.5 (0.7-19.9)	1	6.9 (0.2-38.4)	0	0.0 (0.0-10.5)
Biliary tract	1	2.4 (0.1-13.5)	0	0.0 (0.0-28.9)	0	0.0 (0.0-11.1)
Pancreas	1	1.3 (0.0-7.4)	1	3.6 (0.1-20.0)	0	0.0 (0.0-5.5)
Larynx	1	2.7 (0.1-15.3)	0	0.0 (0.0-24.5)	0	0.0 (0.0-11.2)
Lung ^a	14	3.9 ^a (2.1-6.5)	4	2.8 (0.8-7.2)	9	2.6 ^a (1.2-5.0)
Melanoma of skin ^a	4	5.3 ^a (1.4-13.5)	1	3.1 (0.1-17.0)	1	1.6 (0.0-9.0)
NMSC	18	3.6 (2.1-5.6)	4	2.0 (0.5-5.0)	1	0.2 (0.0-1.1)
Soft tissue	1	7.1 (0.2-39.4)	0	0.0 (0.0-65.5)	0	0.0 (0.0-34.3)
Breast, females ^a	22	7.5 ^a (4.7-11.3)	0	0.0 (0.0-4.1)	2	1.3 (0.2-4.5)
Cervix uteri	3	3.6 (0.7-10.5)	0	0.0 (0.0-11.7)	1	2.2 (0.1-12.0)
Corpus uteri	1	1.0 (0.0-5.7)	0	0.0 (0.0-13.9)	1	2.0 (0.1-11.2)
Ovary	2	2.8 (0.3-10.3)	0	0.0 (0.0-17.1)	0	0.0 (0.0-9.9)
Prostate	2	1.7 (0.2-6.2)	0	0.0 (0.0-5.5)	3	1.8 (0.4-5.1)
Testis	0	0.0 (0.0-16.5)	0	0.0 (0.0-30.5)	0	0.0 (0.0-21.6)
Kidney ^a	6	5.4 ^a (2.0-11.8)	0	0.0 (0.0-8.0)	1	1.0 (0.0-5.5)
Bladder	3	3.5 (0.7-10.3)	0	0.0 (0.0-9.8)	2	2.2 (0.3-7.8)
Brain, spinal cord	0	0.0 (0.0-9.2)	0	0.0 (0.0-22.2)	0	0.0 (0.0-11.9)
Thyroid ^a	5	15.6 ^a (5.1-36.3)	1	7.3 (0.2-40.5)	2	9.3 ^a (1.1-33.8)
HL	0	0.0 (0.0-20.9)	0	0.0 (0.0-45.9)	0	0.0 (0.0-29.6)
NHL ^a	3	5.9 ^a (1.2-17.1)	4	19.4 ^a (5.3-49.8)	8	18.7 ^a (8.1-36.8)
MM	0	0.0 (0.0-18.5)	0	0.0 (0.0-50.2)	0	0.0 (0.0-21.2)
Leukaemia ^a	3	5.6 ^a (1.2-16.5)	2	9.6 ^a (1.2-34.7)	2	4.3 (0.5-15.6)
Other cancers	1	0.8 (0.0-4.4)	1	2.1 (0.1-11.9)	0	0.0 (0.0-3.5)
In situ neoplasms	1	0.8 (0.0-4.5)	0	0.0 (0.0-5.1)	1	1.0 (0.0-5.6)
Uncertain behaviour	2	5.3 (0.6-19.0)	0	0.0 (0.0-20.8)	2	5.7 (0.7-20.6)
All cancers, except NMSC	96	4.0 ^a (3.3-4.9)	19	2.1 ^a (1.2-3.2)	39	1.9 ^a (1.4-2.7)

NMSC, nonmelanoma skin cancer; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; MM, multiple myeloma; No., number of cases; SIR, standardised incidence ratio; CI, confidence interval.

^aIndicates significant result (CI not overlapping 1).

described that 14% of patients developed SC within 25 years after completion of treatment for Hodgkin's lymphoma, which represents 177 cases of SC altogether and 154 cases of second cancer after excluding NMSC, respectively.

The patterns of the most common SC mirrored general cancer incidence with lung and breast cancer being the most frequent (17.5% and 15.6% of all malignancies, respectively). Nevertheless, the highest standardised incidence ratio was observed in non-Hodgkin's

lymphoma (SIR = 13.1) and thyroid cancer (SIR = 11.9). The risk of solid SC development is increased especially by the use of radiotherapy, whereas the risk of secondary leukaemia/non-Hodgkin's lymphomas is increased by the use of alkylating agents (mechlorethamine, cyclophosphamide).⁶ The majority of our patients were treated before 1995, when anthracyclines were not available in our country for political and economical reasons. Therefore, most patients were treated with different combinations of mechlorethamine, vincristine, procarbazine (MOPP) or in combination with cyclophosphamide (COPP) or chlorambucil (LOPP). Nevertheless, some reports indicate, that chemotherapy may even be more cancerogenic as the rate of SC remains the same despite the reduction in radiotherapy field and dosage.^{3,7}

Generally, high incidence of breast cancer is mirrored by the highest absolute excess risk of 30.8 (per 10 000 person-years) even with lower but still significant standardised incidence ratio of 4.4. On the other hand, AER values are showing how massive is excess in the risk of developing these SC. Various types of second cancers were described in different periods after diagnosis of HL as well as after different type of initial treatment.

Patients with HL are generally at greater risk of developing SC. A number of retrospective analyses have been published so far⁸⁻¹⁰ including a meta-analysis assessing 15 randomised clinical trials with as many as 3343 patients.¹¹ Most of these analyses calculated the SIR and AER for the history of the diagnosis of HL itself and compared the incidence of site second cancers in HL patients with the estimated incidence of comparable cancers in the normal patient population. In our analysis, we focused on HL survivors in terms of their treatment and how their treatment may have affected their long-term survival. Taking into account the site of radiation as a risk factor, AER of breast cancer is 46.9 compared to 30.8 AER for the whole Hodgkin's lymphoma population, showing how significant the risk factor using radiation therapy is. Efforts to reduce the risk of SC have led over time to reduce the radiation field to what is currently standard recommendation (so called involved site irradiation).¹² The role of radiotherapy was also evaluated in recently published Cochrane systematic review (individual participant data of patients treated within clinical trials) showing that omission of additional radiotherapy probably reduces SC incidence. Nevertheless, for early stages, reduced field or reduced-dose radiotherapy did not appear to markedly affect efficacy or secondary malignancy risk.⁶ Still, long follow-up is needed to evaluate the effect of currently reduced target volumes as well as reduced safety margins for setup errors reductions, which is currently enabled thanks to technical advances in radiotherapy technology.

The initial stage of the disease also influences the risk of SC. One may assume that patients with early stage of HL are treated in general practice by less aggressive therapies what is consistent with available evidence including further recent Cochrane review.¹³ Moreover, the addition of radiotherapy to chemotherapy has probably little or no difference on OS in early stage HL.¹³ On the other hand, in more advanced stages of HL, there was insufficient evidence to determine the effect of chemotherapy intensification on SC in

TABLE 5 Site-specific risk of second primary malignancy after Hodgkin lymphoma – malignancies within the field of irradiation. The table includes only cancers, where at least one case occurred

Second malignancy	No. n = 92	SIR	95% CI	AER
NMSC ^a	3	15.5 ^a	3.2-45.4	200.3
Thyroid ^a	6	14.1 ^a	5.2-30.8	7.1
NHL ^a	7	10.1 ^a	4.1-20.8	7.5
Liver ^a	3	7.4 ^a	1.5-21.5	3.8
Kidney ^a	3	7.1 ^a	1.5-20.8	12.3
Leukaemia ^a	5	7.0 ^a	2.3-16.3	5.1
Breast, females ^a	22	6.4 ^a	4.0-9.7	46.9
Stomach ^a	7	6.1 ^a	2.4-12.5	7.5
Colon and rectum ^a	8	4.9 ^a	2.1-9.6	22.8
Ovary	1	4.9	0.1-27.3	9.1
Lung ^a	17	4.1 ^a	2.4-6.6	17.0
Cervix uteri	1	3.9	0.1-21.8	8.4
Uncertain behaviour	2	3.7	0.4-13.2	1.7
Corpus uteri	1	3.5	0.1-19.4	8.0
Oral cavity, pharynx	2	2.8	0.3-10.1	2.0
Pancreas	1	2.8	0.1-15.6	2.4
Biliary tract	1	2.3	0.1-12.7	0.8
Other cancers	2	1.2	0.1-4.4	0.5

NMSC, nonmelanoma skin cancer; NHL, non-Hodgkin's lymphoma; No., number of cases; SIR, standardised incidence ratio; CI, confidence interval; AER, absolute excess risk per 10 000 person-years.

^aIndicates significant result (CI not overlapping 1).

general, however, the rate of secondary acute leukaemias was probably higher than among those who had treatment with standard-dose ABVD-like protocols and evidence suggesting improved survival with intensified chemotherapy was not conclusive.⁶ These observations are consistent with long-term results of HD2000 trial of advanced stage HL comparing three different intensified regimes, where lower mortality rates resulting from SC were observed after treatment with less aggressive regimen (ABVD).¹⁴ In our analysis, we did not observe significant correlation of SC and the initial stage. The results of subsequent studies, including trials evaluating the role of immunotherapy, will further expand the understanding of the risk of SC. The role of immune system before therapy is increasingly recognised to determine the general condition of immune surveillance against malignant diseases¹⁵ or prognosis. Pretreatment neutrophil/lymphocyte ratio and platelet/lymphocyte ratio was shown to be prognostic of progression in early stage HL.¹⁶ Current renaissance in immunotherapy will subsequently influence the treatment results and possibly the risk of SC, similarly as in novel treatment approaches in solid cancers.^{5,17,18}

On the basis of our initial analysis of HL survivors,¹⁹ we suggested special follow-up schema for patients after initial HL treatment and utilised this approach in last decade finding it possible, effective and

HL survivors at risk of following secondary cancer	Recommendation for site-specific follow-up
Breast cancer	To follow the American Cancer Society recommendation for high risk breast cancer patients, that is ultrasonography until the age of 40/mammography/MRI once a year, no later than 8 years after completion of radiotherapy or after reaching 30 years of age.
Gastric cancer	Gastroscopy once a year, no later than 10 years after completion of radiotherapy besides standard annual clinical examination
Colon/rectal cancer	Faecal occult bleeding test once a year and colonoscopy whenever any suspicion arises.
Thyroid gland within the radiation field	Serum TSH and FT4 levels examined annually, followed by ultrasonography examination whenever any suspicion arises.
Lung cancer	Active antismoking programme and perform imaging exam in the event of any symptoms. Screening programme, preferably with low dose thoracic CT questionable

HL, Hodgkin's lymphoma; TSH, thyroid-stimulating hormone; FT4, free thyroxine.

acceptable to healthcare providers and payers. The system depends on gender, form of HL treatment and especially the form of radiation therapy in terms of location of radiation fields. Recommended schema is summarised in Table 6.

Our study has several limitations, mainly related to retrospective nature of analysis. From methodology point of view, limitation is in SIR calculation itself and in estimation of cancer incidence rates before 1977, which was assumed equal to those observed in 1977-1979 according to Czech National Cancer Registry. It is also important to acknowledge radiotherapy techniques which were used in our patients. Most of these patients were treated before 1980 with dosages and field setups which are now considered to be outdated. Further, mono-radiotherapy is no currently state of the art treatment in any stage of HL. At that time, extensive radiotherapy fields and the following involved field's definitions were based mainly on bony landmarks and therefore rather rigid concepts. Modern radiotherapy (with so called involved-node and involved-site RT) considers multimodal imaging as well as anatomic changes during therapy.²⁰ With these new approaches, comparing to some older techniques as mantel field technique or inverted-Y irradiation,²¹ one may expect reduced risk of radiotherapy induced SC in the future.^{6,14,15,22,23} Reduced dose to 20 Gy comparing to 30 Gy in early stage HL was also shown noninferior in some randomised clinical trials.²⁴ Nevertheless, there are still many patients surveilled in clinical practice, who were irradiated by these older radiotherapy techniques and with increasing prevalence, there is a need of updated reasonable follow-up schemas as provided in our study. We aimed to describe the whole consecutive cohort of patients treated in general clinical practice outside of clinical trials, what may also bias results considering wide range of stage, dosage of medication used or age of patients. Younger patients are more vulnerable to radiotherapy and may therefore have an increased absolute/relative risk for SC, nevertheless, the incidence of malignancies normally peaks at higher ages and that is why the absolute number of occurring SC (or supposed SC) is much higher when regarding older patients.²⁵

TABLE 6 Recommendations for HL survivors follow-up

In summary, patients with HL are generally at great risk of developing SC, which is significantly increased especially by the use of radiotherapy. Unlike HL, second solid cancers in advanced stages are generally fatal for the patient. Intensive site-specific follow-up to reveal SC in early curable stages is needed to maintain benefit of initial oncology treatment as well as maintain everyday joyful being of our HL survivors for as long as possible.

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DISCLOSURE

The authors have declared no conflicts of interest.

AUTHOR CONTRIBUTIONS

Petrakova: Concept/design, Critical revision of article, Approval of article; Vyskocil: Data analysis/interpretation, Data collection, Critical revision of article, Approval of article; Grell: Data collection, Critical revision of article, Approval of article; Majek: Statistics, Approval of article; Soumarova: Critical revision of article, Approval of article; Novak: Data collection, Approval of article; Burkon: Critical revision of article, Approval of article; Kral: Critical revision of article, Approval of article; Kazda: Critical revision of article, Approval of article, Drafting article; Vyzula: Concept/design, Critical revision of article, Approval of article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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9. Závěr

Léčba HL prošla v posledních desetiletích mimořádně dynamickým vývojem a představuje jeden z nejúspěšnějších příkladů moderní onkologie. Výrazného zlepšení výsledků bylo dosaženo zejména zavedením nových terapeutických postupů, jejichž účinnost a bezpečnost byly následně ověřeny v rozsáhlých mezinárodních klinických studiích. V současnosti tak většina pacientů dosahuje dlouhodobé remise. Cílem moderního terapeutického přístupu již není pouze maximalizace účinnosti, ale současně také minimalizace akutní i pozdní toxicity a zachování co nejlepší kvality života dlouhodobě přežívajících nemocných.

Publikace zařazené do této disertační práce dokumentují jednotlivé etapy tohoto vývoje a zaměřují se na klinicky významné otázky související s optimalizací léčebných strategií. Studie realizované v rámci Německé studijní skupiny pro Hodgkinův lymfom, na nichž jsem se podílel jako spoluautor, přispěly k vytvoření současných standardů léčby časných i pokročilých stadií onemocnění. Studie HD10 prokázala možnost bezpečné deeskalace léčby u pacientů s časným příznivým HL, zatímco studie HD14 potvrdila význam krátké intenzifikace léčby u nemocných s časným nepříznivým onemocněním. Studie HD15 následně optimalizovala léčbu pokročilých stadií zavedením šesti cyklů eskalovaného BEACOPP a PET-řízené indikace konsolidační radioterapie, čímž významně přispěla ke snížení dlouhodobé toxicity při zachování vysoké léčebné účinnosti.

Další publikace zařazené do disertační práce rozšiřují poznatky o významu FDG-PET/CT při hodnocení léčebné odpovědi, o prognostických faktorech ovlivňujících výsledky léčby, o klinickém významu extranodálního postižení, expresi PD-L1, sekundárních malignitách i o možnostech léčby relabovaného a refrakterního HL pomocí brentuximab vedotinu. Tyto práce přispívají k lepšímu pochopení biologické heterogenity onemocnění a podporují individualizaci léčebného přístupu v běžné klinické praxi.

Předložený soubor prací dokumentuje dlouhodobou a aktivní účast autora na vědecké činnosti zaměřené na optimalizaci léčby HL, identifikaci prognostických a prediktivních faktorů a možnosti individualizace terapeutického přístupu. Jednotlivé publikace nepředstavují izolované studie zaměřené na nesouvisející problematiku, ale naopak dokumentují postupný vývoj odborného zaměření autora – od aktivní účasti na

mezinárodních klinických studiích až po vlastní klinický výzkum zaměřený na identifikaci prognostických a prediktivních markerů využitelných při individualizaci léčby. Vzájemná tematická a časová návaznost jednotlivých prací odráží vývoj moderního přístupu k léčbě HL, od standardizovaných léčebných postupů směrem k terapii zohledňující biologické charakteristiky nádoru a individuální riziko konkrétního nemocného.

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