How to treat localized Hodgkin lymphoma?

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Purpose of review
We aim to summarize the current knowledge on the management of early-stage classical Hodgkin lymphoma, with a focus on conventional strategies, incorporation of immunotherapies and exploration of novel prognostic markers.

Recent findings
Long-term data on combined modalities (associating chemotherapy and radiotherapy) still supports their benefit in terms of progression free survival compared to chemotherapy alone in both early favourable and early unfavourable interim PET-negative classical Hodgkin Lymphoma. Novel agents, such as Brentuximab Vedotin and checkpoints inhibitors show promising and impressive results when added to first-line treatment. Various strategies have been used, mainly in phase 2 non randomized clinical trials. Interim PET-scan has limited prognostic value and its role in regimens incorporating immunotherapies is yet unknown. Other prognosis markers emerge, such as metabolic tumour volume and circulating tumour DNA. By reflecting tumour burden pretreatment and minimal residual disease on treatment, they might be useful tools guiding treatment decisions.

Summary
Novel immunotherapy agents are likely to change the landscape in front-line management of classical early-stage Hodgkin lymphoma by combined modality treatment. Despite encouraging recent data, proof of their efficacy and safety on the longer term are still needed. Treatment decisions might be guided by new promising prognosis markers but their use in clinical practice is still to be determined.

Keywords
brentuximab vedotin, checkpoint inhibitors, ctDNA, early-stage, Hodgkin lymphoma, metabolic tumour volume

INTRODUCTION

Early-stage classical Hodgkin Lymphoma (cHL) is curable in most patients. Management differs according to disease extension and presence of risk factors. Localized forms are therefore divided into two categories: early favourable (stages I-II without risk factor) and intermediate or early unfavourable (stages I–II with risk factors). It is important to note that risk factors slightly differ between the different cooperative groups (Table 1).

Historically, most approaches used a combination of chemotherapy and radiotherapy (combined modalities, CMT). But rapidly, attention about long-term toxicity risk mostly following radiotherapy (RT) has been raised [1]. More specifically, the risk of secondary malignancies and cardio-vascular diseases proved to be concerning [2,3].

Positron emission tomography-computed tomography (PET-CT) emerged as an important prognostic factor in the management of early-stage disease. Sparing RT for patients reaching interim PET (iPET) negativity after 2 cycles of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) was investigated in multiple trials. However, disease control in the early favourable group appears to be better with the use of localized RT, as demonstrated in the HD16, RAPID and H10 trials. All three failed to demonstrate noninferiority of PET-guided omission of radiotherapy in terms of progression free survival (PFS) for those patients [4,5,6].

Omission of radiotherapy in the early unfavourable group has also been tested. The H10 trial showed that noninferiority could again not be demonstrated for iPET-negative patients, although less strikingly than in the favourable group [6]. RT-free regimens, more suitable for patients such as young female with large mediastinal mass, do however exist. The HD17 trials showed that RT could safely

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KEY POINTS

- Radiotherapy still plays an important role for disease control in early favourable classical Hodgkin lymphoma (cHL). Despite not bringing significant difference in terms of overall survival, higher PFS can translate into better quality of life for the patients.
- When choosing amongst conventional treatments, clinicians must balance the risk of potential late toxicities with the risk of relapse in their patients.
- The addition of Brentuximab Vedotin to chemotherapy could provide a safe and efficient radiotherapy-free regimen and an alternate option to eBEACOPP, but larger randomized trials are needed.
- Strategies using checkpoint inhibitors show high efficacy and excellent short-term PFS and OS, but larger randomized trials are also needed to guide clinical practice.
- The predictive role of PET-scans in the era of immunotherapy combinations remains undefined and might be completed or replaced by other markers, such as TMTV and ctDNA.

be omitted for patients reaching iPET-negativity after two cycles of eBEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone) and two cycles of ABVD [7], while the RATHL approach offers a de-escalation to four cycles of AVD (adriamycin, vinblastine, dacarbazine) for patients reaching iPET-negativity after two cycles of ABVD [8].

New therapies in cHL now incorporate immunotherapies such as the antibody drug conjugate Brentuximab-vedotin (BV) and checkpoints inhibitors (CPI). In this review, we will summarize how those contemporary treatments are changing the landscape for localised disease and how they compare to more conventional therapies.

LONG-TERM DATA ON THE INTERIM PET RESPONSE ADAPTED STRATEGY

Recently, long-term follow-up of the H10 and HD16 trials have been published. As a reminder, at time of both publications, noninferiority of radiotherapy omission could not be demonstrated in both favourable and unfavourable groups reaching iPET negativity after two cycles of ABVD [4,6]. The 10-year analysis of the H10 trial still supports the initial findings and showed PFS rates of 98.8% (favourable) and 91.4% (unfavourable) when treated with involved-node radiotherapy (INRT; 30 Gy) vs. 85.4% (favourable) and 86.5% (unfavourable) when treated with chemotherapy alone [9]. In the HD16 trial, the 5-year PFS for iPET-negative patients was also higher with CMT than with chemotherapy alone (94.2% vs. 86.7%) [10▪]. Interestingly, both groups noted that the vast majority (between 79% and 91%) of the relapses occurred in previously involved non irradiated locations [9,10▪], highlighting the important role of RT on disease control.

Despite those differences in PFS, no significant difference in overall survival was noted between CMT and chemotherapy alone (CT) strategies, with numbers reaching above 98% at 5 years in the HD16 trial [10▪] and above 94–98% at 10 years in both groups of the H10 trial [9], questioning benefits brought by radiotherapy.

Real-world data comparing CMT and CT is limited. A large retrospective American cohort of early stages cHL showed that the proportion of patients receiving CMT decreased from 58% in 2004 to 34% in 2017 and was associated with a statistically significant decrease in overall survival (OS), reaching 93.5.% at 10 years with CMT vs. 88.7% with CT [11▪]. Another study suggested that favourable, nonbulky or iPET-negative patients could safely omit RT, but that unfavourable, bulky, or iPET-positive diseases had better outcomes with CMT [12].

Table 1. Risk factors according to cooperative treatment groups

	EORTC-LYSA [28]	GHSG [29]	NCCN [30]
Risk factors	Mediastinal mass	A) Mediastinal mass	Bulky disease
	Age ≥50 years	B) Extranodal site	Any B symptoms
	ESR ≥50 or ≥30 if B symptoms	C) ESR ≥50	ESR >50
	≥4 nodal areas	D) ≥3 nodal areas	>3 involved sites
Stage:			
favourable	I–II without risk factor	I–II without risk factor	I–II without risk factor
Unfavourable (or intermediate)	I–II with ≥1 risk factor	I–II with ≥1 risk factor and IIB with C/D without A/B	I–II with ≥ 1 risk factor

EORTC, European Organization for Research and Treatment of Cancer; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group; LYSA, Lymphoma Study Association; NCCN, National Comprehensive Cancer Network.

Most appropriate management for iPET-positive patients after two cycles of ABVD is still open to debate. The H10 trial suggested to switch to two cycles of eBEACOPP and to consolidate with INRT (30 Gy), following an improved 5-year PFS of 90.6% vs. 77.4% for continuing with ABVD + INRT [6]. The 10-year PFS rate is still higher with eBEACOPP (85.1% vs. 79.2%), but no longer statistically different [9]. Ten-year overall survival rates were similar in both arms, at 90.4% and 92% [9]. Reassuringly, escalation to BEACOPP + INRT did not show safety alerts and the amount of late toxicities were similar compared to the ABVD + INRT arm. In particular, incidence of cardiovascular toxicities was respectively 9.3% vs. 7.7% and incidence of secondary malignancies 4.7% vs. 4.6% [9]. Both the RAPID and the HD16 trials did not opt for chemotherapy intensification in case of positive iPET but offered more ABVD with involved-field RT at the doses of 30 (RAPID) or 20 (HD16) Gy. They reached 5-year PFS of 87.6% and 88.4%, respectively [4,5].

INCORPORATING BRENTUXIMAB VEDOTIN INTO FIRST-LINE TREATMENT

Reed-Steinberg cells were found to universally express CD30 [13], making them a target for Brentuximab Vedotin (BV), an antibody-drug conjugate consisting of an anti-CD30 immunoglobulin G1 (IgG1) antibody and a microtubule-disrupting antimitotic agent (monomethyl auristatin E).

Incorporating BV to first-line treatment was introduced after proof of high activity in the relapsed/refractory setting. One of the intentions behind adding BV in early-stage diseases is to assess if radiotherapy can be safely omitted. Numerous prospective phase 2 trials have been published so far, with different strategies and inclusion criteria.

Abramson *et al.* conducted two phase 2 trials using BV for stages I/II nonbulky cHL. After adding BV to AVD with an iPET response assessment strategy in 36 patients [14], they further dropped vinblastine and used a brentuximab vedotin, adriamycin, dacarbazine (BV–AD) combination in 34 patients [15▪▪]. Designs were similar in both studies and consisted of 2 cycles of BV–A(V)D followed by two (iPET-negative) or four (iPET-positive) more cycles of BV–A(V)D, without RT. iPET-positive rates were low (0–6%) and both approaches led to impressive PFS and OS rate (BV–AVD: 3-year PFS and OS rates of 94% and 96% respectively. BV–AD: 5-year PFS and OS rates of 91% and 97%). From a toxicity perspective, the BV–AD regimen showed an interesting profile, with no grade ≥ 3 peripheral neuropathy and no febrile neutropenia without preemptive use of G-CSF. Similar toxicities occurred in respectively 24% and 29% of the patients when BV–AVD was used. Those encouraging results seem to indicate that adding BV to chemotherapy not only might provide a RT-free regimen but could also allow for the omission of two cytotoxic drugs in localized nonbulky cHL.

BV added to a chemotherapy backbone has also been tested in patients with early-stage bulky disease. Kumar *et al.* included 116 patients with early unfavourable cHL according to the GHSG criteria and divided them in 4 cohorts [16]. All patients received 4 cycles of BV-AVD and were either consolidated with RT (cohorts 1–3, various fields and doses) or not consolidated at all (cohort 4). Two-year PFS rate reached 96.6% in the RT-free cohort and was similar to the 2-year PFS rates observed in the radiotherapy cohorts (89.7–96.6%), indicating again that omitting RT might be safely done when BV is added to AVD.

Another strategy is the use of BV as a consolidation after ABVD. It was tested in a phase 2 trial developed by Park *et al.* including 40 patients with stages I/II nonbulky cHL. Treatment was initiated with two cycles of ABVD before a new treatment decision based on iPET (negative PET indicated by a Deauville score ≤ 2) and risk factors (favourable disease defined by the absence of B symptoms, ESR < 50 or ≤ 3 sites of disease) [17]. Favourable and iPET-negative patients were immediately consolidated with 6 cycles of BV while the other groups benefited from more ABVD (two more cycles for the favourable/iPET-positives and the unfavourable/iPET-negatives; four more cycles for the unfavourable/iPET-positive patients) before the consolidation with 6 cycles of BV. RT was offered to the end of treatment (EoT) PET-positive patients only. PFS and OS at 3 years were high: 92% and 97% respectively and even reached 100% for EoT PET-negative patients. Only 2 patients were offered RT.

Despite all being promising, none of those trials are randomized. The only randomized trial incorporating BV for early-stage cHL is the phase 2 BREACH trial, comparing four cycles of BV-AVD + 30 Gy INRT vs. four cycles of ABVD + 30 Gy INRT in early unfavourable patients, without PET-adapted strategy [18▪▪]. One hundred and seventy patients were enrolled in a 2 : 1 randomization ratio in favour of BV-AVD. Primary endpoint was the rate of iPET-negativity and it proved to be increased with BV-AVD (82.3% compared to 75.4% for the ABVD arm). Two-year PFS were respectively 97.3% and 92.6%. A significantly reduced 2-year PFS was noted in iPET-positive group treated with ABVD (71.6%), compared to BV-AVD (93.8%), showing a possible alternative to eBEACOPP. However, by systematically consolidating with RT, this approach did not address the question of whether RT could be omitted in early unfavourable patients treated with BV-AVD.

The phase 3 RADAR trial, focusing on early-stage cHL without B symptoms or mediastinal bulk and comparing ABVD vs. BV-AVD with iPET-adjusted response, is currently recruiting. It will aim at answering the question of RT omission in early-stage patients (ClinicalTrials.gov identifier: NCT04685616).

INCORPORATING CHECKPOINT INHIBITORS INTO FIRST-LINE TREATMENT

Importance of tumour microenvironment in cHL is well known and Reed-Steinberg cells were found to evade immunity through the overexpression of programmed cell death-1 ligands (PD-L1), allowing for T-cell inhibition and tumour cells survival [19]. The PD-L1/PD-1 axis can be targeted by check-points inhibitors (CPI) such as nivolumab, tislelizumab and pembrolizumab.

Nivolumab was explored in the GHSG NIVAHL phase 2 randomized trial. It focused on early unfavourable patients and compared concomitant administration of nivolumab plus AVD (N-AVD) for four cycles vs. a sequential treatment with 4 fortnightly infusions of nivolumab followed by 2 cycles of N-AVD and 2 cycles of AVD [20▪▪]. All patients later benefited from consolidation with 30 Gy ISRT. Management was not influenced by iPET; however, one was performed after 4 cycles of N-AVD or 4 infusions of Nivolumab. Interestingly, more than half of the patients (51%) reached a complete metabolic response (CMR) after being treated with immunotherapy only, highlighting tumoricidal effect of Nivolumab on its own. Both arms allowed for high rates of CMR (83–84%) at the end of treatment. Three-year PFS and OS rates are comparable at 98–100%. Toxicity profile is manageable, but 17% of patients had persisting hypothyroidism. Despite looking promising, those results do not address the possibility of omitting RT nor the possibility of de-escalating treatment based on iPET response.

The ongoing phase 2 INDIE trial (ClinicalTrials.gov Identifier: NCT04837859) will try to answer both questions. Early-stage unfavourable patients will be started on Tislelizumab for two doses before disease assessment with iPET. In case of favourable response (iPET negative), a chemo-free management will be attempted with 4 further cycles of Tislelizumab. In case of iPET-positivity, patients will then receive four cycles of Tislelizumab plus AVD. Consolidation with involved-site RT (30 Gy) will only be offered to EoT PET-positive patients.

A third CPI, pembrolizumab, has also been evaluated, sequentially to or concurrently to AVD in both advanced and localized cHL. The sequential administration consisted of Pembrolizumab monotherapy for 3 doses (every fortnight) before four cycles of AVD in the early unfavourable group (as per NCCN criteria) [21]. The concurrent regimen consisted of 6 cycles of AVD+P [22]. All-stages cHL were included and a fifth of the cohort were early unfavourable patients. The sequential approach led to an impressive 100% rate of CMR reached after Pembrolizumab induction and two cycles of AVD. Both 3-year PFS and OS also reached 100% [21]. Results of the sequential approach were equivalently interesting with 2-year PFS and OS rates of 97% and 100%, respectively [22].

IMPROVING PROGNOSTIC MARKERS

Up until now, iPET-scans were used as the most important prognostic factors in the management of early-stage cHL. Their positive predictive value has however been estimated to be as low as 30–50% [23▪], highlighting a need for better prognostic markers.

Metabolic tumour volume (MTV), which is the metabolically active volume of the tumour determined on baseline PET-scans, has proven to be a moderate predictive factor in both early favourable and early unfavourable cHL when treated with conventional combined modalities [24,25▪,26]. The calculation method has however not yet been standardized and is therefore not reproductible in clinical practice. In the BREACH study, a threshold of 147cm^3 has been used to define high total MTV (TMTV). With seven out of eight relapses having high TMTV, it was found to have a strong prognostic value on the outcome [18▪▪]. Furthermore, the proportion of patients with high TMTV who relapsed was lower in the BV-AVD arm compared to the ABVD arm, suggesting that they might benefit more from the addition of BV.

Circulating tumour DNA (ctDNA) has also recently been explored as a predictive marker, showing strong potential pre, on-, and posttreatment [18▪▪,27▪▪]. Indeed, in a recently published paper, Alig *et al.* observed that TMTV is highly correlated with ctDNA levels and that patients with high ctDNA levels at diagnosis had significantly shorter PFS. They also showed that patients with durable remissions had lower ctDNA levels at various times during treatment and that ctDNA detection after treatment is significantly associated with the risk of relapse [27▪▪].

The ongoing phase 2 RAFTING trial (ClinicalTrials.gov Identifier: 04866654) will combine those promising prognostic markers. With an iPET and MTV-adapted strategy in early stages non bulky cHL, they aim to assess feasibility and safety of RT omission for patients with a very low risk of treatment failure (negative iPET after 2 ABVD and low MTV). They will also continue to explore the role of MRD detection by cell-free circulating DNA analysis.

CONCLUSION

Overall, while currently validated treatment options already offer reassuring PFS and OS rates in localized cHL, various strategies using immunotherapies show even more impressive results and very attractive PFS and OS rates. Numbers of patients treated are however still low, and proof of efficacy on the longer term still needs to be demonstrated. Toxicity profiles appear to be manageable but need to be monitored cautiously in a mainly young population with little to no comorbidities prior to starting treatment.

Ideal treatment modality, including or not conventional chemotherapy or radiotherapy has not been established yet. iPET was until now a strong predictive factor, helping to tailor each patient's management plan. Its role with novel agents is still to be determined and might be completed or replaced with new markers, such as ctDNA and TMTV.

While we may wonder if we are reaching maximum cure rate for localized classical Hodgkin lymphoma, we cannot forget about long-term toxicities and treatment burden.

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