



Limited Stage DLBCL: current management and challenges

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Title Page
Limited Stage DLBCL: current management and challenges

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Limited stage DLBCL: current management and challenges

Abstract (200 words)

25-30% of diffuse large B-cell lymphoma (DLBCL) presents as limited stage (I-II). Prognosis is generally excellent with 4-6 cycles of R-CHOP alone (rituximab, cyclophosphamide, vincristine, doxorubicin, prednisolone) or combined modality therapy with 3-4 cycles and involved site radiotherapy (RT). There is growing interest in optimising algorithms to retain disease control whilst minimizing long-term toxicity, with several recent studies focusing on the safety of abbreviating chemotherapy and omitting RT in low risk patients and the utility of PET-based response-adapted approaches. As these studies are limited to younger patients without risk factors, application of similar approaches in elderly or higher risk patients is hampered by a lack of evidence. Whilst there has been a move away from using RT in low risk patients, it remains a useful adjunct in specific situations. Current evidence cannot exclude a clinically meaningful benefit from RT even in low risk patients and, given the low expected toxicity from modern RT techniques, a risk-benefit assessment should be individualized and considered in a multidisciplinary fashion. The optimal approach for extranodal limited stage DLBCL (~40% of cases) varies according to site of origin. Herein we discuss the latest clinical trial evidence and how this can be applied in routine practice.

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Introduction and historical context

Limited stage diffuse large B-cell lymphoma (DLBCL) is usually defined as stage I-II according to the Ann-Arbor staging system meaning that disease is restricted to above or below the diaphragm. Stage II patients with bulk (although often not bulky stage I) were usually excluded from historic clinical trials (1).

25-30% of DLBCL presents with limited stage disease. Whilst the prognosis is excellent with modern therapy, a continuous pattern of relapse has been described (2, 3). Adverse risk factors are summarised in the stage-modified international prognostic index (smIPI). This index includes age over 60 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2 or more, stage II, and elevated lactate dehydrogenase (LDH) (4). The 5-year progression-free survival (PFS) can be divided according to this scoring system (smIPI 0=97%, 1-2=86%, 3=30%) (5).

Before the development of effective combination chemotherapy, radiotherapy was frequently employed as a single-modality treatment and whilst often effective in stage I disease with durable remission rates of over 60%, stage II disease fared much less well with frequent relapses (6). Earlier studies using combination chemotherapy alone, usually with at least 8 cycles of cyclophosphamide, vincristine and prednisolone (COP) and COP with doxorubicin (CHOP) in patients for whom radiotherapy was not deemed appropriate, also showed durable, high remission rates (7). These studies did not use CT or PET scanning for staging and the histological classification systems were different from those currently used. Despite this, the principle of potential cure with radiotherapy or chemotherapy was established. Combined modality therapy (CMT) where

3-4 chemotherapy cycles were combined with radiotherapy, was then evaluated and durable remissions in >80% was reported (8). Patients included in this analysis had stage I and II disease, no B symptoms and no bulk disease (defined as maximum tumour diameter of 10 cm or more, or no more than one third of the maximum intrathoracic diameter for mediastinal masses).

During the late 1980s and 1990s, one of 2 approaches was usually followed based on these early studies. One involved treatment with chemotherapy alone, usually following the approach for advanced stage patients, with 6-8 cycles of CHOP. The other approach combined reduced CHOP cycles with involved field radiotherapy (IFRT). Arguments could be made in favour of each approach. Chemotherapy alone avoided the potential for late effects of radiotherapy including cardiovascular disease and second cancers which were becoming increasingly apparent in cohorts treated for Hodgkin lymphoma, whereas increased cycles of chemotherapy were associated with their own toxicity including both short-term (e.g. febrile neutropenia) and long-term (e.g. anthracycline-induced cardiac damage). The South West Oncology Group (SWOG) performed a randomised study (SWOG Study 8736) to formally compare the two approaches (4). Over 400 patients were enrolled with low-risk stage I or non-bulky stage II disease [75% DLBCL, 72% smIPI=0-1]; 37% had extranodal lesions and 29% had all visible tumour resected during diagnostic work-up. Eight cycles of CHOP were compared with 3 cycles plus 40-55 Gray (Gy) of IFRT. Both PFS and overall survival (OS) were prolonged in the CMT group (5-year PFS estimates 77% v 64%; 5-year OS estimates 82% v 72%) and significantly more life-threatening toxic effects were observed in the chemotherapy alone arm although this was before the introduction of granulocyte colony stimulating factor (G-CSF). This trial effectively established CMT (3 cycles of CHOP and radiotherapy) as the standard of care for early stage DLBCL. Although the initial PFS and OS advantage of CMT was lost after longer follow-up (2) CMT has, until recently, remained the international 'standard of care' for limited-stage DLBCL.

In the early 2000s, the addition of rituximab to chemotherapy led to superior outcomes in the phase III MabThera International (MINT) Trial (9). 823 young, low-risk DLBCL patients were randomly assigned to six cycles of CHOP-like chemotherapy with or without rituximab. Patients with bulky or extranodal disease also received radiotherapy. Chemoimmunotherapy was superior to chemotherapy alone with a superior 6-year event-free survival (EFS), PFS and OS, without worse acute or long-term toxicity, including secondary malignancies. This study established the addition of rituximab to chemotherapy in low-risk, early stage DLBCL although the trial did not adopt a strategy of abbreviated CHOP (+/- rituximab) with radiotherapy.

More recent studies, such as the SWOG 0014 and FLYER trials, confirmed that both CMT in the rituximab era and abbreviated immunochemotherapy are associated with excellent outcome in low-risk patients.

SWOG 0014

In this study, excellent outcomes are described with 3 cycles of R-CHOP and IFRT at 40-46 Gray (Gy). Sixty patients with aggressive, CD20-expressing non-Hodgkin lymphoma (NHL) with at least one adverse factor

based on the smIPI (93% DLBCL, 70% smIPI=1, 30% smIPI=2-3) were enrolled (10). This phase II non-randomised trial was prior to the era of PET-based risk adaptation. 2- and 4-year PFS and OS was 93% and 88%, and 95% and 92%, respectively. This reinforced CMT (abbreviated R-CHOP with IFRT) as a standard approach for limited stage DLBCL.

FLYER Trial

Recently, the results of the FLYER randomised phase III trial were published (3). FLYER showed that 4 cycles of R-CHOP plus 2 additional doses of rituximab is non-inferior to 6 cycles of R-CHOP in young patients (≤ 60 years) with low-risk [normal LDH, ECOG PS 0-1, bulk < 7.5 cm, 99% age-adjusted IPI (aaIPI=0)], limited stage aggressive CD20-positive B-cell NHL (85% DLBCL). After a median follow-up of 66 months, 3-year PFS was 96% (95% confidence interval (CI) 94%-99%) with 4 cycles of R-CHOP plus two cycles of rituximab versus 94% (95% CI 91%-97%) with 6 cycles of R-CHOP. The absolute difference between groups in 3-year PFS was 3% (lower limit of the one sided 95% CI 0%). The 95% CI was on the positive side of the pre-specified non-inferiority margin of -5.5% . This demonstrated that 4 cycles of R-CHOP plus two cycles of rituximab was non-inferior compared to 6 cycles of R-CHOP. There was no OS difference between the approaches. There were fewer adverse events in the 4-cycle group, including grade 3-4 leucopenia, infection, nausea, vomiting and mucositis. Therefore, on the basis of FLYER, abbreviating treatment to 4 cycles of R-CHOP is considered safe in DLBCL patients ≤ 60 years without risk factors as defined in the FLYER inclusion criteria. It is unclear whether the two additional doses of rituximab confer benefit beyond 4 cycles of R-CHOP. Although FLYER effectively demonstrates the safety of immunochemotherapy de-escalation in these low risk patients it does not exclude the possibility of a small net benefit from RT in some circumstances, e.g. bulk disease (> 5 cm) and/or with a predicted low risk of RT toxicity, e.g. unilateral neck or groin disease.

PET-adapted approaches in limited stage DLBCL

The favourable prognosis of the majority of cases of limited stage DLBCL raises the question as to whether therapeutic algorithms could be response-adapted and treatment minimised with the goal to retain disease control and minimise long-term toxicity. There is growing interest in a response-adapted strategy, whereby treatment is reduced in patients with chemo-responsive disease without compromising efficacy and/or escalated early in patients with resistant disease with the attempt to improve outcome. Table 1 provides a summary of recent key clinical data.

A number of studies have evaluated the predictive value of interim positron emission tomography (iPET) in advanced stage DLBCL, with conflicting results. In this setting the negative predictive value (NPV) of iPET for disease progression generally exceeds 80%, the positive predictive value (PPV) ranges between 20%-74% (11). The high false-positive rate of $\sim 25\%$ can be due to inflammation, infection, tumour necrosis and scanning too soon following chemo/radiotherapy. The predictive value of iPET is higher the later it is applied during the treatment (12). These estimates of NPV and PPV may not necessarily apply to limited stage DLBCL in whom PET is typically performed at the end of chemotherapy. No study has yet shown in a randomised comparison,

an improvement in outcome using an end of chemotherapy PET-based response-adapted strategy in limited stage DLBCL compared to a standard approach. However, recent studies incorporated the PET-adapted approach in limited stage DLBCL. These are discussed below.

SWOG NCTN S1001

In this non-randomised prospective trial (5), 132 patients with non-bulky (<10cm) limited-stage disease (median 62 years, smIPI 0=27%, 1=42%, 2=28%, 3=4%) received 3 cycles of R-CHOP, followed by a PET. Patients with a negative PET proceeded with 1 additional R-CHOP, whereas those with a positive PET received IFRT followed by ibritumomab tiuxetan. Of the 128 patients that underwent PET assessment, 11% were positive. With a median follow-up of 4.9 years, the 5-year PFS (87%) and OS (89%) were similar in PET-positive and PET-negative patients.

British Columbia Cancer Centre (BCCC) Retrospective Data

In the BCCC, patients with non-bulky (<10 cm in this institution) limited stage DLBCL have been treated according to a PET-guided algorithm since 2005. A PET-CT is performed following 3 cycles of R-CHOP. Patients with a negative PET receive one additional cycle of R-CHOP, while PET-positive patients received involved-site RT (ISRT). Sehn and colleagues (13) recently presented the long-term data with a median follow-up of >6 years. Of the 319 patients (median 68 years, smIPI 0=19%, 1=45%, 2=27%, 3-4=9%) who received 3 cycles of R-CHOP, 80% patients were PET-negative, 18% were PET-positive and 2% were considered PET-indeterminate (by International Harmonisation Project criteria). The overall 5-year PFS was 84% for all patients (88% for PET-negative and 74% for PET-positive patients) and 5-year OS was 87% for all patients (90% for PET-negative and 77% for PET-positive).

LYSA/GOELAMS PET-adapted trial

A recent randomised study by the LYSA/GOELAMS French group compared R-CHOP alone to R-CHOP plus IFRT (40 Gy) in 334 non-bulky (defined as < 7 cm), low-risk, limited stage DLBCL patients aged 18 to 75 years (94% mIPI 0 or 1, 64% age ≤ 60 years) (14). Patients without any adverse prognostic factors (normal LDH, stage I, PS = 0, age <60 years, mIPI = 0) received 4 cycles of R-CHOP-14, whereas those with ≥1 adverse prognostic factors (high LDH, stage II, PS >0, age >60, mIPI ≥1) received 6 cycles. Patients who achieved partial metabolic response (PMR) by PET-CT after cycle 4 R-CHOP were recommended to receive two additional cycles followed by IFRT, regardless of which treatment arm they were initially allocated. All other responding patients (i.e. those obtaining a complete metabolic response (CMR) after 4 cycles of R-CHOP) followed the initial planned randomisation. The 5-year EFS and OS were not statistically significantly different between the arms (89% vs. 92% and 92% vs. 96%). There were 13 relapses in the R-CHOP alone arm (5 at the initial site), and 10 in the R-CHOP plus RT arm (none within the initial irradiated field). Lamy and colleagues (14) concluded that IFRT could be omitted in low-risk, non-bulky limited stage DLBCL achieving a CMR after 4 cycles of R-CHOP. It is important to note that this trial was only powered for an 8% EFS non-inferiority margin and excluded bulky (>7cm) DLBCL. As such it is difficult to exclude a residual meaningful benefit for IFRT in this context. Additionally, 44%

of those obtaining CMR with a mIPI \geq 1 received 6 cycles of R-CHOP with the associated increased risk of anthracycline toxicity that may exceed RT-related risks.

OPTIMAL >60 trial

For older patients, the ongoing OPTIMAL >60 trial is currently assessing the safety of abbreviated course of R-CHOP in patients >60 years considered fit for full dose R-CHOP (15). Patients aged 61-80 years with an IPI of 1 without bulk (<7.5 cm) were randomised to 4 cycles of R-CHOP-14 or 4 cycles of R-CHLIP-14 (liposomal vincristine) plus 4 additional doses of rituximab. Patients with a positive PET after 4 cycles received 2 additional CHOP/CHLIP-14 plus ISRT (39.6 Gy). A planned interim analysis compared patient outcome to that of 74 matched, limited stage RICOVER-60 patients, who had received 6 cycles of R-CHOP-14 plus 2 additional rituximab doses (16). Despite enrolling older patients, the outcome of the OPTIMAL >60 patients presented were non-inferior to that of the RICOVER-60 matched cohort [2-year PFS 94% vs. 90%]. 82% achieved a CMR after 4 cycles and received no further treatment. The outcome of the 18% of PET-positive patients was similar to that of PET-negative patients following 2 additional R-CHOP/CHLIP-14 plus ISRT. The OPTIMAL>60 trial did not include IFRT as a randomisation and, whilst the interim results appear impressive compared to historical controls, this study does not directly exclude a residual role for modern low-toxicity radiotherapy.

Overall, these studies demonstrate that most patients with limited-stage DLBCL are PET negative after 3-4 cycles of R-CHOP and have excellent outcomes with 4 cycles of chemotherapy alone without additional RT which may offer a small increase in local control (5, 13-15). Patients with a positive PET have a slightly less favourable or comparable survival outcomes with the addition of radiotherapy with or without additional chemotherapy/radioimmunotherapy. However, without a large randomised comparison between PET-adapted and conventional approach, it is unclear from these studies how PET contributes to improving the outcome of a group that already has excellent prognosis. The number of PET positive patients in these trials is small (10-20%), making it difficult to draw conclusions regarding the contribution of treatment escalation to their prognosis.

The results of the Lymphoma Academic Research Organisation randomised study (NCT01285765) comparing a PET-adapted algorithm with standard treatment of low risk (aIPI = 0) limited stage DLBCL (18-80 years) are awaited. This is the first randomised study comparing PET-adapted and conventional approaches (recruitment completed May 2020). The primary endpoint is 3-year PFS with the aim to demonstrate non-inferiority of the PET-adapted arm. All patients will have an early evaluation with an interim PET after 2 cycles, repeated after 4 cycles. In the standard arm, the patients receive 6 R-CHOP-21 regardless of PET results. In the experimental arm, early responders (PET negative after 2 cycles, confirmed after 4 cycles) will receive a total of 4 cycles of R-CHOP-21. In both arms, if PET remains positive after 4 cycles of R-CHOP, biopsy is done to confirm residual disease and escalation to more intensive treatment is recommended. This study is primarily designed to demonstrate non-inferiority of PET-based treatment de-escalation from 6 cycles of R-CHOP to 4 cycles of R-CHOP, in a patient group recently shown to have excellent prognosis when treated with 4 cycles of R-CHOP.

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Studies to date have established that PET-based treatment de-escalation is safe and the ongoing randomised study aims to confirm that it is non-inferior to a conventional approach. However, due to the poor PPV of PET, it remains unable to specifically identify the small minority of limited-stage patients with resistant disease, and to date, it has not been shown that treatment escalation based on PET improves outcome compared to conventional approach.

Table 1 summarises the key recent clinical data. Figure 1 outlines our suggested pathway for front line treatment of limited stage DLBCL based on the currently available evidence discussed above.

Role of radiotherapy in limited stage DLBCL

Any decision regarding the role of modern radiotherapy compared to additional cycles of chemotherapy requires an understanding of the varying toxicities and benefits of these approaches. For example, it is important to consider the risk of cardiac toxicity of anthracycline exposure with additional chemotherapy (17) compared to the risk of radiotherapy in an individual patient. Unlike Hodgkin lymphoma, there is no strong evidence for an increased second cancer risk due to radiotherapy in this patient group, even in historical cohorts (18). Any late toxicity risks of radiotherapy are anticipated to have declined substantially over the last two decades with the reduction in prescribed dose to 30 Gy (19), reduction in irradiation volumes with involved-site principles (20) and with improved techniques of radiotherapy delivery.

Large population-based cohort studies suggest the potential value of CMT over chemotherapy alone. For example, Vargo and colleagues (21) analysed almost 60,000 patients with localised DLBCL treated between 1998 and 2012. The rate of CMT declined from 47% in 2000 to 32% in 2012 ($p<0.001$). Interestingly, the 5- and 10-year OS rates were 75% and 55% for chemotherapy alone and 82% and 64% for CMT ($p<0.001$). This effect persisted in the period 2008 to 2012, an era where PET scanning would have been more commonly used.

Radiotherapy remains the standard of care post-chemotherapy for patients with ‘bulky’ DLBCL at diagnosis. The accepted definition of bulk in DLBCL varies in the literature and is often $>7.5\text{cm}$ or even $>10\text{ cm}$. However, evidence for the prognostic significance of bulk from the MInT study (22) found that there was a linear relationship between maximal tumour dimension (MTD) and the risk of an event between 5 cm and 10 cm. There was no evidence for a cut-off, neither for EFS nor OS. A number of recent trials, including FLYER, excluded patients with bulk (e.g. 7.5cm in FLYER) (3). It therefore remains reasonable to consider offering RT to patients with bulky localised DLBCL; with the definition of bulk varying depending on the data considered. There are other specific sites in localised DLBCL where RT should be routinely recommended such as testicular involvement (23, 24) and others, such as bone, where it should be considered for added local control. The management of extranodal DLBCL is discussed later in more detail.

Although recent studies suggest that local radiotherapy is not necessary to obtain excellent outcomes in low risk, limited stage DLBCL, a number of these studies did not include RT or were not adequately powered to exclude the possibility of modest, but potentially clinically meaningful, benefits from RT. As discussed, population based data suggest this approach may be negatively affecting survival (21) and any estimates of late radiation-related side effects must be carefully considered on an individualised basis.

Immunochemotherapy alone in limited stage DLBCL is a very reasonable approach in younger patients (<60 years) with no risk factors (PS/IPI=0 and MTD<5 cm) or where there are particular individualised concerns regarding RT risk.

Limited stage DLBCL in the elderly

Despite some improved understanding the management of elderly patients presenting with DLBCL, it remains the case that few specific analyses and no prospective clinical trials have focused on the management of limited stage DLBCL in elderly patients. Although the recent S1001 trial (5) had an older population (median 62 years) than other recent prospective trials (3, 14), all were considered fit for full dose R-CHOP prior to enrolment.

The role of anthracycline-based immunochemotherapy - most commonly attenuated 'mini' R-CHOP (cyclophosphamide 400 mg/m², doxorubicin 25 mg/m², vincristine 1 mg) (25-28) - has become an established standard of care in older DLBCL patients. Two recent LYSA prospective phase II trials primarily focused on patients with advanced stage disease. These trials enrolled 23-25% of elderly (>80 years) patients with limited stage DLBCL (bulky stage I was eligible). Patients with limited stage I-II DLBCL in the initial R-mini-CHOP LYSA trial had a numerically but not statistically significant improvement in OS compared to advanced stage DLBCL (55.9% vs 68.5%, p=0.17) (27). Staging was not included within the multivariable analysis, but aIPI was included and it was not a significant determinate of OS. Patients were also enrolled within the ofatumumab plus mini-CHOP phase II study with a lower aIPI. Age-adjusted IPI 0-1 vs 2-3 had a marked improvement in 2-year OS (82% vs 56%, p<0.0001) however again aIPI was not analysed specifically by its component parts (26). Neither of these studies mandated PET-staging at baseline.

Although large retrospective series in elderly DLBCL patients have documented the inferior PFS (25, 29-31) in advanced stage III-IV DLBCL as opposed to early stage I-II DLBCL, detailed analyses focused on the specific management of the early-stage patients has not to date been performed.

Together these data provide mixed evidence suggesting that elderly patients with limited stage DLBCL may have improved PFS and OS compared to patients with advanced stage DLBCL when treated with 6 cycles of attenuated R-CHOP. Despite the improved toxicity profile associated with cycle number reduction, none of these studies discussed have specifically addressed the questions that have been examined in younger patients regarding a) the role of PET-CT response-adapted therapy, b) the optimal cycle number when

attenuated dosing is used, and c) the role of radiotherapy. There is a clear need to evaluate these key questions in prospective studies of elderly patient populations with stage I-II DLBCL who may not be fit for full dose R-CHOP. At present, there is therefore no strong evidence to enable confident reduction of cycle number from 6 cycles to 3-4 cycles of R-mini-CHOP in elderly patients with limited stage I-II DLBCL. It is however recognised that radiotherapy can be a particularly valuable adjuvant therapy in combination with R-mini-CHOP in the elderly, particularly in bulky disease, due to a lower concern regarding long-term side effects combined with an increased importance of immediate improvements in disease control. It may also be useful when considering fewer cycles of chemotherapy due to toxicity concerns (32, 33) or patient/physician preference (Figure 1).

Management of CNS prophylaxis in limited stage DLBCL

The majority of patients with limited stage DLBCL by definition present with a low or intermediate CNS international prognostic score (CNS-IPI) (34). Most of these patients, particular those with nodal DLBCL, have a particularly low CNS relapse risk and therefore CNS prophylaxis is not warranted. Specific extranodal disease sites have been variably associated with CNS relapse risk in the literature and remain somewhat controversial. These include epidural, orbital, craniofacial or bone involvement. There is however no strong evidence for increased risk of CNS relapse in the rituximab era for isolated disease at these sites (35). Stage IE isolated testicular DLBCL is a relatively common presentation of limited stage DLBCL in older males and as discussed is strongly associated with CNS relapse risk (24). Strategies are outlined in the relevant section of this review, and should include CNS prophylaxis (23). Although intrathecal prophylaxis alone was used within this prospective phase II IELSG trial, strong consideration should be given to the inclusion of high dose methotrexate alongside intrathecal therapy in CNS prophylaxis algorithms for this specific indication in appropriately selected patients (36).

More uncommon but clinically important high risk extranodal sites where CNS prophylaxis is often recommended include breast (37), renal, adrenal (34, 38, 39) or uterine involvement (40). It is very unusual for renal, adrenal or uterine involvement to occur as isolated stage IE disease. Involvement of these sites occurs more commonly in patients presenting with advanced stage, high risk DLBCL. For example, only 3/17 patients with uterine involvement had limited stage DLBCL in recent series focused on CNS relapse risk of female reproductive organ DLBCL involvement. Ovarian involvement was not associated with increased CNS relapse risk in this series (40).

Disease site-specific considerations

Population data suggests 40% of DLBCL present with extranodal disease as their main clinical presentation. Patients with extranodal disease are typically older with poorer performance status albeit with a lower disease burden (41). Most of the larger studies of early stage DLBCL include patients with stage IE and IIE disease. However, significant biological differences exist between specific primary extranodal DLBCLs and their nodal

counterparts (42, 43) meaning that the optimal approach may vary (Figure 1). Four primary extranodal areas will be considered here: primary testicular, gastric, bone and breast lymphoma.

Primary testicular lymphoma (PTL)

PTL is considered to be associated with a worse clinical outcome than many other subtypes of DLBCL. It is characterised by a high risk of central nervous system (CNS) relapse and involvement of the contralateral testis (24, 44) leading to the recommendation for CNS prophylaxis and adjuvant scrotal irradiation. Although most patients present with stage I or II disease, little data exists regarding an abbreviated chemotherapy approach. In the largest retrospective analysis performed by the IELSG, outcome did appear worse for patients receiving <6 cycles of chemotherapy (10-year OS 44% vs 19%; $p=0.03$) although most patients in this study did not receive rituximab (24). A subsequent phase II trial using R-CHOP treated all patients with at least 6 cycles of chemotherapy (23). Currently, there is insufficient data to suggest abbreviated chemotherapy for this group of patients. Of note, 11 patients with PTL were enrolled in the FLYER trial: 3 patients relapsed, 2 of whom had had 6 cycles of R-CHOP, 1 of whom had had 4 cycles (3). Such small numbers however cannot lead to a change in practise and 6 cycles remains the standard of care.

Primary gastric DLBCL

The approach to treating primary gastric DLBCL confined to the stomach is generally similar to treating other sites of localised disease with either 6 cycles of R-CHOP or 3-4 cycles with radiotherapy depending on risk profile. However, a few specific considerations require discussion. Eradication of *Helicobacter pylori* (HP) alone has been reported to induce remission in some patients with localised HP positive gastric DLBCL; both in cases with evidence of residual mucosa-associated lymphoid tissue (MALT) lymphoma and in those without (45-47). One study reported on 50 patients with HP positive stage IE/IIIE primary gastric DLBCL who were treated with upfront HP eradication. They observed a CR rate of 69% in those with *de novo* DLBCL and 56% of patients with DLBCL transformed from MALT lymphoma (48) with no relapses at a median follow up of 7.7 years. Further work suggested that the expression of the cytotoxin-associated gene A (CAG-A) and its signalling molecules may predict for responding patients (49). Whilst an HP eradication approach alone is practised in some centres and is reasonable given published results, it must be done with caution, regular monitoring and early intervention with immunochemotherapy if signs of progression or response failure emerge. HP eradication alongside other therapy is very reasonable due to its safety and tolerability.

Another point of debate has been the role of surgery. Whilst surgery undoubtedly can play a role if life-threatening complications develop such as perforation, uncontrollable bleeding or fistula formation, its role in disease control is more controversial. Several large studies suggest its role in this setting is limited. A retrospective study of 272 patients from China (50) suggested that whilst patients treated with chemotherapy without rituximab did less well than those who underwent surgery, the group treated with immunochemotherapy did not have inferior outcomes. A large prospective study in Brazil prior to routine use of rituximab also showed surgery was not associated with superior outcomes and occasional fatal

complications were observed (51). In the R-CHOP era, surgery is therefore not routine practise for disease control outside of the emergency setting.

Primary bone lymphoma (PBL)

Lymphoma affecting the bone as the predominant site is an uncommon presentation with the most frequent histology being DLBCL (52). Published data regarding the management of early stage PBL is sparse and largely consists of series which span many years, with variable inclusion of rituximab to chemotherapy (which was usually CHOP) (43, 53, 54). One of the largest series was the IELSG-14 study, which reported on 161 patients with PBL mostly with stage IE. The estimated 5-year PFS was 68%. In this analysis, neither radiotherapy following chemotherapy, nor higher doses nor wider fields of radiotherapy were associated with improved outcomes. However, results from other studies are conflicting with some suggesting a benefit of CMT (54). Only one prospective study focused on this group (55) and used 3 cycles of CHOP combined with 45 Gy of radiotherapy. The study was slow to recruit and terminated early with only 33 patients enrolled. A 5-year OS rate of 90% with a local control rate of 72% was observed. Based on limited data therefore, 3 cycles of R-CHOP with radiotherapy, or 6 cycles of R-CHOP with or without radiotherapy are both reasonable approaches for PBL.

Primary Breast DLBCL

Although other subtypes of lymphoma can arise within the breast, DLBCL is the commonest (56, 57). The IELSG published a series of 204 patients treated in the pre-rituximab era (58). Key observations included no benefit from mastectomy compared with diagnostic biopsy or lumpectomy and a propensity to relapse at extranodal sites including the ipsilateral or contralateral breast (16%) and in the CNS (5%); findings which have been confirmed in other series (37, 59). Primary CNS prophylaxis is often recommended due to the CNS relapse risk and radiotherapy due to the local relapse risk. In support of radiotherapy in the rituximab era, an analysis from the Surveillance, Epidemiology and End Results (SEER) database of 386 patients demonstrated an improved OS rate for those who received radiotherapy (60). Six cycles of chemotherapy is also frequently delivered, supported by the IELSG study showing a benefit for more than 3 cycles, although this benefit was less evident in the patients who received an anthracycline containing combination (58). In a more recent retrospective study of 68 patients in which nearly all were treated with an anthracycline and most with rituximab, fewer than 4 cycles of chemotherapy was associated with reduced PFS on multivariate analysis with or without local treatment (61). Although the quality of data is relatively low, 6 cycles of R-CHOP with consolidation radiotherapy and CNS prophylaxis is generally considered optimal.

In conclusion, the management of limited stage DLBCL has developed greatly over recent years with a number of clinical trials enhancing our understanding of how best to manage patients. The applicability of each given trial requires a clear understanding of the aims of the study and the patient characteristics enrolled in each trial. The FLYER and recent LYSA/GOELAMS trials have given the treating community confidence that it is safe

to reduce the number of cycles of R-CHOP from 6 to 4 and omit radiotherapy within a pre-specified low risk population without bulk. Involved site radiotherapy remains a useful adjunct in all other situations and should be particularly considered for bulky disease, in the elderly where attenuated chemotherapy dosing is used and in extranodal limited-stage presentations. All decisions regarding the duration of R-CHOP, the role of radiotherapy and the need for other adjunctive therapy, such as CNS prophylaxis, require detailed discussion within expert multidisciplinary team meetings, with careful consideration of varying benefits and risks of each approach and involvement of the patient in the decision-making process.

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For Peer Review

Study	Treatment arms (n)	Inclusion criteria	Histology/stage	Median age (years)	ECOG PS	LDH >ULN	Bulk	Extranodal involvement	IPI	Median follow up	Response rate	PFS	OS
Poeschel et. al (2019)(1) Phase 3, open-label, non-inferiority RCT (FLYER)	R-CHOP x4 +2R (n = 293) vs. R-CHOP x6 (n = 295) Non-inferiority margin -5.5%	Age 18-60 years, stage I/II, ECOG PS 0-1, LDH normal, no bulk (<7.5 cm), aggressive B-NHL	85% DLBCL, stage I/II (99%)	48 (range 18-60)	0-1 (100%)	0%	<1%	32%	aalPI = 0 (99%)	66 months (IQR 42-100)	91% vs. 92% CR/CRu; 3% vs. 4% PR; 0% vs. <1% SD	96% vs. 94% at 3-years; 94% vs. 94% at 5-years	99% vs. 98% at 3-years; 97% vs. 98% at 5-years
Pfreundschuh et. al (2017)(2) RCT (OPTIMAL >60)	4x CHOP-14 vs. CHLIP-14 + 8x R If PET positive – additional 2x CHOP/CHLIP + ISRT (39.6 Gy)	Age 61-80, IPI = 1 (age >60 years), no bulk (<7.5 cm)	-	71	-	-	-	-	-	-	-	94% at 2-years vs. 90% in RICOVER-60 [HR 0.5 (95% CI: 0.2-1.5) p=0.208]	98% at 2-years vs. 91% in RICOVER-60 [HR 0.2 (95% CI: 0.1-0.9) p=0.036]
Persky et. al (2020)(3) Phase 2, prospective cohort (NCTN S1001)	R-CHOP x3 PET negative (89%) +R-CHOP x1 PET positive (11%) +IFRT (36 Gy) +ibritumomab tiuxetan (n = 132 eligible, n = 128 had iPET)	Age >=18 years, stage I/II, WHO PS 0-2, no bulk (<10 cm)	72% DLBCL NOS. 17% high-grade B-cell lymphoma NOS, stage I (62%)	62 (range 18-86), (54% >60)	0-1 (97%)	14%	-	43%	smIPI = 0 (27%), 1 (42%), 2 (28%), 3 (4%)	4.92 years (range 1.1-7.7)	92% CR, 4% PR, 1% SD	87% at 5 years (89% PET negative, 86% PET positive)	89% at 5 years (91% PET negative, 85% PET positive)
Lamy et. al (2018)(4) RCT, LYSA/GOELAMS	R-CHOP-14 +/- IFRT (40 Gy) R-CHOP x4 if no RF R-CHOP x6 if RF or PR after 4 cycles (n = 334)	Age 18-75 years, stage I/II, no bulk (<7 cm), DLBCL	-	36% >60 years	0-1 (97%)	18%	-	39%	smIPI 0-1 (94%)	64 months (range 24-132)	CR 94% (no RT) vs. 98% (with RT)	EFS 89% vs 92% at 5 yrs [HR 0.61 (95% CI: 0.3-1.2) p= 0.18]	92% vs. 96% at 5 yrs [HR 0.62 (95% CI: 0.3-1.5) p = 0.28]
Sehn et. al (2019)(5) Retrospective cohort, BC Cancer	R-CHOP x3 PET negative (80%) +R-CHOPx1 PET positive (18%) +IFRT (n = 319)	Stage I/II, no bulk (<10 cm), DLBCL	Stage I (59%), stage II (41%)	68 (range 19-92)	0-1 (92%)	13%	≥5 cm (37%)	52%	smIPI = 0 (19%), 1 (45%), 2 (27%), 3-4 (9%)	6.25 years (0.42-14.25)	-	84% at 5 years (88% PET negative, 74% iPET positive)	87% at 5 years (90% PET negative, 77% iPET positive)

Table 1. Summary of recent key clinical data

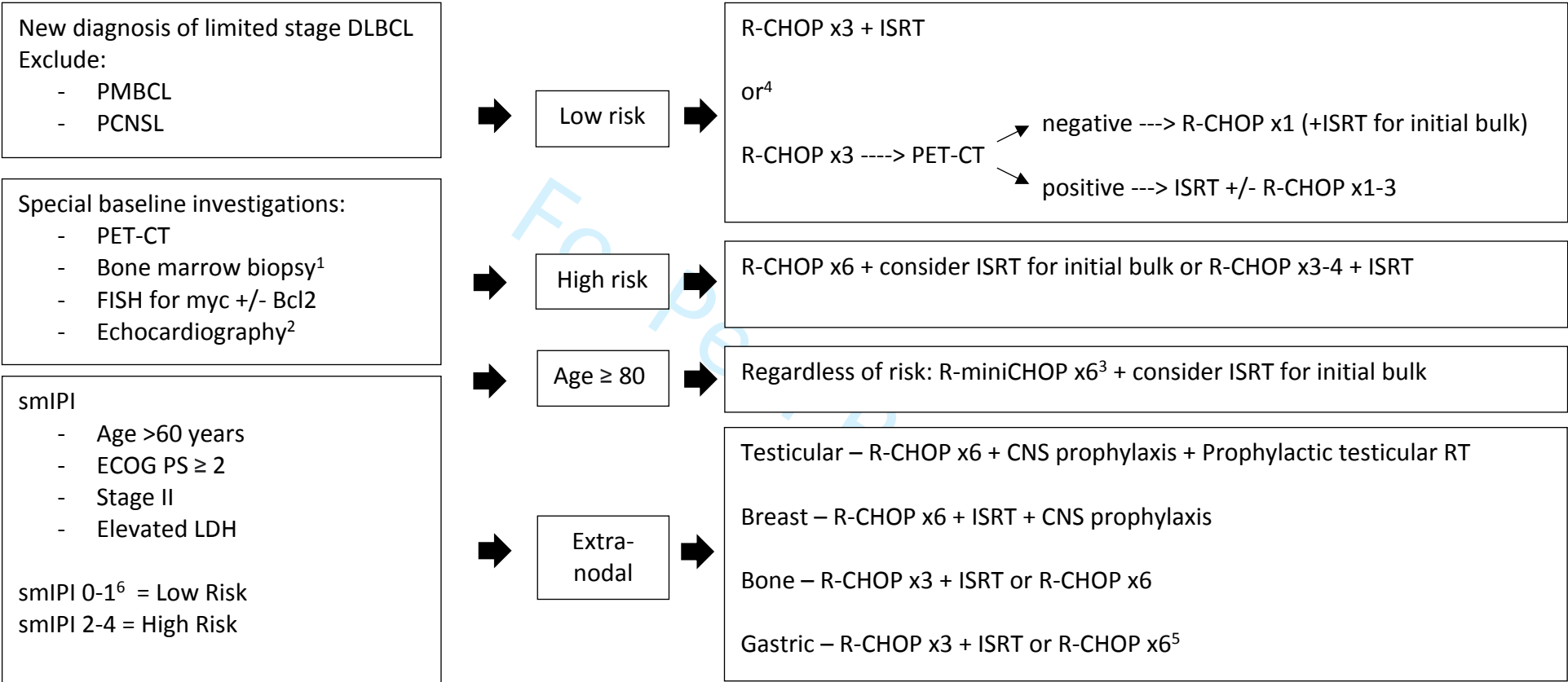
Abbreviations:
aalPI (age-adjusted IPI), BC (British Columbia), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), CHLIP (cyclophosphamide, doxorubicin, liposomal vincristine, prednisolone), CI (confidence interval), CR (complete response), CRu (complete response unconfirmed), DLBCL (diffuse large B-cell lymphoma), ECOG PS (Eastern Cooperative Oncology Group performance status), EFS (events free survival), HR (hazard ratio), iPET (interim positron emission tomography), IPI (international prognostic index), IFRT (involved-field radiotherapy), IQR (inter-quartile range), ISRT (involved-site radiotherapy), LDH (lactate dehydrogenase), OS (overall survival), PFS (progression free survival), PR (partial response), R (rituximab), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone), RCT (randomised controlled trial), RF (risk factor – high LDH, stage II, PS >0, >60 years, smIPI ≥1), SD (stable disease), smIPI (stage-modified IPI), ULN (upper limit normal), WHO (World Health Organisation)

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Figure 1. Pathway for front line treatment of limited stage DLBCL
If available consider clinical trial



¹Optional – not needed to confirm involvement by high grade lymphoma if PET scan performed.
²If > 70 years of age or any risk factor for ischaemic heart disease.
³There is no evidence for giving fewer than 6 courses of R-miniCHOP in early-stage disease although maybe done with subsequent RT if not tolerating chemotherapy.
⁴There is currently no evidence that the PET-adapted approach is superior to conventional combined modality treatment.
⁵Close follow up with no chemotherapy or RT is an option.
⁶The LYSA/GOELAMS trial included only smIPI 0 patients, whereas the FLYER trial included stage II patients (i.e. smIPI 0-1).
Abbreviations: DLBCL: diffuse large B cell lymphoma, R-CHOP: rituximab, cyclophosphamide, vincristine, prednisolone, ISRT: involved site radiotherapy, PMBCL: primary mediastinal B cell lymphoma, PCNSL: primary central nervous system lymphoma, FISH: fluorescence in situ hybridisation, smIPI: stage-modified international prognostic index, CNS: central nervous system, RT: radiotherapy