Extranodal Localization of Aggressive Lymphoma

10

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10.1 Introduction

Aggressive lymphomas with primary extranodal origin can be found in virtually all extranodal sites [1–6]. In fact, no less than 25% of diffuse large B-cell lymphomas (DLBCLs) primarily arise in a site other than a lymph node or lymphoid organ [7]. There are some discrepancies in the definition of primary extranodal lymphoma that may contribute to the wide range in the incidence described for these cases [6, 8–11]. Whereas the situation is clear for localized lymphomas isolated to a single extranodal location, secondary extranodal involvement by a systemic lymphoma cannot always be ruled out in advanced stage disease. Although definitions have varied, for practical terms lymphomas with a dominant extranodal component and only minimal nodal disease can be considered primary extranodal [6, 8]. Secondary lymphoid organs such as the spleen and Waldeyer's ring, including the tonsils, are typically not considered extranodal sites.

In addition to primary extranodal cases, extranodal involvement is common in typical nodal lymphomas, with around one half of diffuse large B-cell lymphoma (DLBCL) patients showing one extranodal site and 20% two or more. The latter is considered a poor risk parameter in the majority of prognostic scores for aggressive lymphomas, including the International Prognostic Index (IPI) [12–15]. Additionally, DLBCL arising in immunocompromised patients, including HIV+ and posttransplant [16, 17], constitutes distinct biologic subsets with frequently extranodal localization, including the central nervous system (CNS); these lymphomas are reviewed in detail in Chaps. 8 and 9.

The distribution of extranodal sites in aggressive lymphoma is very heterogeneous. The gastrointestinal (GI) tract is the most frequent extranodal site, particularly the stomach, followed by the skin, bone, and CNS. Other sites are rare but include the liver, lungs, and genitourinary organs [4–8, 11]. Within aggressive lymphomas, certain cytogenetic abnormalities increase the likelihood of extranodal involvement. Cases with a MYC translocation, especially in concert with a BCL2 and/or BCL6 rearrangement (so-called double- or triple-hit lymphoma), often involves extranodal locations, including the CNS [18–20].

Staging of primary extranodal DLBCL is similar to nodal DLBCL [21–23], including a PET/CT scan as per the Lugano criteria [23]. Nevertheless, some sites require specific techniques, such as MRI for CNS lymphomas or

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endoscopies with or without endoscopic ultrasound for GI cases. Primary extranodal DLBCL limited to a single extranodal location is considered stage IE or IIE in the setting of local nodal extension only. If extranodal involvement occurs in the setting of either diffuse nodal or additional extranodal sites, then the stage is IV [4, 5, 23].

The aim of this chapter is to review the unique characteristics and treatment approach for patients with the most common primary extranodal aggressive lymphomas. Most correspond to DLBCL, but other histologies, including mantle-cell lymphomas (MCL), Burkitt lymphomas (BL), and peripheral T-cell lymphomas (PTCL), will be also covered. Overall, treatment depends primarily on the histology and, therefore, immunochemotherapy; usually the standard regimen R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone) is the gold standard in most DLBCL cases, irrespective of the nodal or extranodal origin [24]. Nevertheless, some specific consideration should be mentioned for each subtype for the most frequent extranodal sites, including the GI tract, bone, breast, testis and ovary, skin, and primary mediastinal. CNS lymphomas are addressed separately in Chap. 10.

10.2 Gastrointestinal (GI) Lymphomas

GI lymphomas represent 30–40% of all extranodal cases and 5–20% of all non-Hodgkin lymphomas [1, 25, 26]. The stomach is the most frequently involved organ, followed by the small intestine and colon [1, 6, 25, 26]. DLBCL is the predominant histology, representing 60% of gastric and 70% of intestinal lymphomas [27]. Other aggressive histologies include BL (5% of cases) and MCL (5% of cases, in most cases showing the characteristic multiple lymphomatous polyposis) [26].

Patients with aggressive GI lymphomas may present with abdominal pain, dyspepsia, nausea and vomiting, obstruction, or GI hemorrhage. The diagnosis is determined by tissue biopsy, usually obtained in the course of an endoscopic evaluation [7]. Routine staging includes a full body PET/CT scan, as in other aggressive lymphomas; as well as endoscopy (esophagogastroduodenoscopy or colonoscopy), sometimes combined with endoscopic ultrasound which may provide additonal information on depth of invasion and local nodal extension. Notably, aggressive gastric lymphomas, even with bulky presentation, frequently are localized, with no infiltration of any other organ outside GI and regional lymph nodes [6].

10.2.1 Gastric Lymphomas

As already indicated, the stomach is the most frequently involved GI site. DLBCL represents the vast majority of cases, but concomitant MALT lymphoma can also be seen in approximately half of the cases [29]. These cases are often seen in association with *H. pylori* infection, which should be checked in all patients at diagnosis, and may present with symptoms of gastric ulceration including pain or bleeding.

R-CHOP remains the gold-standard treatment for gastric DLBCL [1, 24–30]. Nevertheless, some aspects, including the role of surgery or radiotherapy, and the eradication of *Helicobacter pylori* (HP) deserve further discussion. Prior to the development of effective chemotherapy, surgery with total or partial gastrectomy was considered the standard treatment. Currently, however, the role of surgery is marginal, except in the setting of severe but unusual complications including perforation or refractory hemorrhage [31, 32]. Local therapy with involved field radiotherapy (IF-RT) has also been used but is not considered appropriate monotherapy in gastric lymphomas, even for localized disease, since the risk of relapse is much higher without systemic therapy. Radiation can be considered as local consolidation after chemotherapy, where combined modality does appear to reduce the rate of local relapse but without improvement in overall survival [33]. Notably, this trial was in the pre-rituximab era and no experience has been

published in patients receiving chemoimmunotherapy. *H. pylori* eradication must also be considered in *H. pylori*-positive aggressive gastric lymphomas, as is the gold standard for gastric MALT lymphomas, usually as the only treatment modality. In *H. pylori*-positive DLBCL, however, *H. pylori* eradication is usually considered an adjunct to standard immunochemotherapy. Interestingly, *H. pylori* eradication alone has been preliminarily investigated in gastric DLBCL [34–37]. Two clinical trials have shown high CR rates (63–69%) in de novo limited-stage gastric *H. pylori*-positive DLBCL, as well as in patients with DLBCL arising from *H. pylori*-positive MALT lymphoma (CR rate 56%) [35, 36, 38]. These intriguing data warrant further evaluation but do not presently support antibiotic therapy alone in *H. pylori*-positive DLBCL patients who can tolerate chemoimmunotherapy.

10.2.2 Intestinal Lymphomas

Intestinal lymphomas are the second in frequency within the GI tract. Most cases are DLBCL, although BL, MCL, and PTCL (especially enteropathy-associated T-cell lymphoma) are also seen. MCL is associated with a characteristic syndrome of multiple lymphomatous polyposis, which may be asymptomatic or be associated with discomfort or bleeding.

Diagnosis of intestyinal lymphomas may be made endoscopically, but surgery may also have a role in the diagnosis of intestinal lymphoma (laparoscopy or open surgery with bowel resection) as well as in dealing with complications of the lymphoma itself or sequelae of treatment, including perforation, hemorrhage, or obstruction [39, 40]. R-CHOP is the standard for intestinal DLBCL. The risk of complications is higher than for gastric cases, about 20–30% of cases, and so patients must be followed closely and counseled accordingly.

MCL involvement is usually secondary in the setting of extensive systemic disease and should be treated with the standard approach of this type (chemoimmunotherapy including cytarabine followed by intensification with autologous stem cell transplantation for young fit patients) [41]. At present, the systematic investigation of gastric and colonic involvement by means of endoscopies is not formally recommended for all patients with MCL, since the finding of infiltration does not substantially change prognosis or treatment in this disease which is virtually always advanced stage at the time of diagnosis [42].

Sporadic BL, the predominant subtype seen in Western countries, often presents as a bulky abdominal mass, with the ileocecal area being the most frequently involved location [43]. HIV-associated Burkitt lymphoma will usually present at advanced stage with extensive involvement of virtually any extranodal location [44]. Curative treatment of BL is typically with intensive multi-agent chemotherapy and rituximab. Dose-adjusted EPOCH-R is emerging as a less intensive and highly effective alternative, particularly in older or less fit patients [45].

Finally, primary intestinal T-cell lymphoma is usually diagnosed as enteropathy-associated T-cell lymphoma and occurs in patients with underlying celiac disease [46]. The small intestine is the most commonly involved location, and patients typically present with abdominal pain and diarrhea and may have malabsorption with anorexia, fatigue, and malnutrition. The diagnosis is usually made via endoscopic biopsy. Less commonly, a primary intestinal T-cell lymphoma can occur in the absence of underlying celiac disease, known as intestinal T-cell lymphoma NOS, and also follows an aggressive clinical course. Although localized in the bowel, the prognosis of patients with primary intestinal T-cell lymphomas is generally unfavorable, with a median OS of less than 1 year in multiple series [47]. CHOP-like therapy remains the most popular approach, followed by consolidation with autologous or allogeneic stem cell transplantation in younger patients with a favorable performance status [47–49].

10.3 Primary Bone Lymphoma

Lymphomas primarily arising in bone represent about 5% of extranodal lymphomas and 5% of bone cancers. Histologically, 70–80% are DLBCL, although other histologies are possible, including BL and anaplastic large-cell lymphomas (ALCL), among others [50–53]. Symptoms are usually local, including pain (80–90% of the cases), presence of tumor mass, or pathologic fractures. Osteolysis, hypercalcemia, or spinal cord compression is possible but infrequent. Three forms of presentation are described: a single bone lesion, a polyostotic location with multiple bone lesions, and disseminated lesions in the setting of secondary bone infiltration of a systemic lymphoma [50, 51].

The diagnosis is by means of a bone biopsy. Fine needle aspiration is not sufficient to reach the correct diagnosis and characterization of the lymphoma, so diagnosis usually needs a core needle or surgical biopsy. Plain radiographs are nonspecific, so CT scans or magnetic resonance imaging (MRI) is often employed to define the local extension as well as the cortical invasion and destruction. PET/CT is the standard modality for staging, as for any other DLBCL, with the PET component being particularly important as bone involvement by DLBCL may not sufficiently distort cortical anatomy sufficiently to be obvious on CT alone. PET is also critical in the restaging setting where FDG-avidity is necessary to distinguish active lymphoma from posttreatment sclerotic change [54]. Notably, low-level FDG-avidity posttreatment is common in primary DLBCL of bone due to low-level avidity within sites of bone remodeling following therapy and may need to be followed with serial imaging to insure resolution. Staging is performed with the Lugano criteria where a single bony location is classified as stage IE and mutifocal bone disease classified as stage IV [11]. Patients with localized primary bone DLBCL (stage IE) typically have an excellent outcome, and the usefulness of the IPI may be lower in this subset relative to other DLBCLs [50]. The International Extranodal Lymphoma Study Group (IELSG) found that younger age, normal LDH, good performance status, combined modality therapy, and higher radiation dose predicted particularly favorable outcome [50, 51, 55]. R-CHOP followed by consolidative radiation therapy should therefore be considered the preferred therapy in limited-stage DLBCL of bone if the site is amenable to radiation therapy with an acceptable toxicity profile. For advanced stage disease, R-CHOP remains the cornerstone of therapy for six complete cycles [24, 30]. Data from the German High Grade Lymphoma Study Group has suggested that radiation consolidation to bony sites adds value even in advanced stage disease with an improvement in event-free survival, though without a statistical improvement in OS [56]. Further analysis is required to understand if patients in a complete metabolic remission by PET scan garner benefit from consolidation following chemoimmunotherapy or whether the value of radiation may be limited to PR patients.

10.4 Primary Mediastinal B-Cell Lymphoma

Primary mediastinal B-cell lymphoma (PMBCL) is a distinct clinical and biological variant of DLBCL derived from thymic B cells. Transcriptional profiling has shown that PMBCL shares overlapping molecular features with the nodular sclerosis variant of classical Hodgkin lymphoma (NSHL), including activation of the nuclear factor-kappa B (NF-kB) pathway and Janus kinase/signal transduction and activator of transcription (JAK/STAT) signaling [57–59]. Amplification of the 9p24.1 locus containing JAK2 as well as PD-1 ligands further promotes JAK/STAT activation and immune escape, respectively.

Biologic similarities with NSHL may be reflected histologically as well with the diffuse proliferation of malignant lymphocytes separated by compartmentalizing fibrosis [60]. The malignant cells are often pleomorphic, and Reed-Sternberg-like variants may be observed. Unlike the classical Hodgkin lymphoma, the pan B-cell markers CD19, CD20, CD22, and CD79a are

expressed in PMBCL, though surface immunoglobulin is typically absent. Most cases will also express CD23 and CD30, though the latter is usually dim and heterogeneous in contrast to NSHL where it is bright and uniform. Most cases will express PD-L1 and PD-L2, reflecting the underlying amplification of the 9p24.1 genetic locus.

Clinically, PMBCL occurs in younger patients than typical DLBCL NOS with a median age of approximately 35 years. There is a slight female predominance, and three quarters of patients will present with bulky mediastinal disease. Mediastinal tumors may be locally invasive of midline mediastinal structures, the lungs, pericardium, and chest wall, and can result in superior vena cava syndrome as well as pleural or pericardial effusions. Despite the locally invasive nature, advanced stage disease is uncommon, occurring in only approximately 20% of cases at diagnosis. When disease does occur outside of the mediastinum, disseminated nodal or bone marrow involvement is markedly less common than visceral metastatic disease.

Prior to the introduction of rituximab, the traditional CHOP regimen had been associated with a higher failure rate than would be expected in a large-cell lymphoma occurring predominantly in young people with limited-stage disease. Retrospective analyses of more intensive regimens such as MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) and VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) appeared superior to CHOP [61–63]. The majority of patients in historic series also received consolidative mediastinal radiation, which was associated with an improved progression-free survival compared to patients treated with radiation alone [61, 62]. In the modern era, rituximab added to CHOP may not obviate the deficits of CHOP alone. A retrospective analysis of 63 PMBCL patients treated with R-CHOP reported a 21% incidence of primary induction failure and a 5-year PFS of 68% [64]. Adverse prognostic factors in this analysis included advanced stage disease, older age, and increased age-adjusted IPI score. As in the pre-rituximab era, the majority (77%) of R-CHOP-treated patients received consolidative mediastinal radiation. A subset analysis of 87 patients with PMBCL treated in the prospective Mabthera International Trial (MInT) of CHOP-like chemotherapy with or without rituximab found a benefit for rituximab plus chemotherapy compared to chemotherapy alone [65]. The 3-year event-free survival for patients treated with R-CHOP was excellent at 78%, though notably the trial was limited to patients under the age of 60 with no more than one IPI risk factor, so 92% of subjects had limited-stage disease and the vast majority of high-risk patients who may have fared poorly were excluded. As with prior series, over 70% of subjects also required consolidative radiation therapy. The failure rate with R-CHOP, particularly in high-risk patients, as well as the long-term potential side effects of radiation therapy including secondary malignancies, heart disease, lung disease, and thyroid dysfunction or cancer, prompted further investigation of more intensive regimens combined with rituximab. Dose-adjusted EPOCH-R was evaluated in a phase II study from the National Cancer Institute which included 51 patients with PMBCL treated with 6 cycles of DA-EPOCH-R and no planned radiation therapy. The 5-year event-free survival was 97%; only two patients required radiation treatment, and no patient experienced relapse [66]. These data suggest that DA-EPOCH-R carries a low rate of primary induction failure, appears to obviate the need for irradiation in most patients, and has resulted in a widespread adoption of this treatment as initial therapy in PMBCL.

Though most patients with PMBCL will be cured with frontline chemo-immunotherapy, a significant minority will have primary refractory disease or relapse after achieving initial remission. Most treatment failures occur early—either during initial treatment or within 1 year of completing therapy—and relapses greater than 18 months from completing frontline therapy in this disease are rare. Relapsed and refractory PMBCL is a challenging disease as patients are often resistant to second-line therapy as well. The current approach to relapsed or refractory PMBCL is identical to DLBCL whereby second-line

chemoimmunotherapy is administered, and patients with chemosensitive disease then proceed to high-dose chemotherapy with autologous stem cell transplantation. Unfortunately, PMBCL patients do not fare as well with this traditional salvage approach as other patients with DLBCL [67, 68]. A retrospective analysis of patients with relapsed PMBCL compared to DLBCL NOS found lower rates of overall response to second-line therapy (25% versus 48%) and worse overall survival at 2 years (15% versus 34%) [68]. Novel therapies are therefore needed for these high-risk patients at relapse. Expression of CD30 in the majority of tumors prompted investigation of brentuximab vedotin, a CD30-directed antibody drug conjugate, which is highly effective and FDA approved for treatment of relapsed classical Hodgkin lymphoma, a biologic cousin of PMBCL. Unfortunately, the results of a phase II study in relapsed PMBCL were disappointing with objective responses observed in only 2 of 15 treated patients in a phase II study, both partial responses, prompting early closure of the trial [69]. More appealing has been targeting the amplified PD-L1 and PD-L2 with immune checkpoint inhibitors, as has also proven effective in relapsed classical Hodgkin lymphoma. A prospective phase II study of the PD-1 inhibitor pembrolizumab included 17 evaluable patients with PMBCL and showed responses in 7 of 17 patients (41%) [70]. The median duration of remission had not been reached at a median follow-up of 11 months, suggesting that many of these responses may prove durable. Finally, anti-CD19 CAR T-cells have shown the ability to induce complete and durable remissions in a significant proportion of patients with chemorefractory PMBCL and are now considered the standard therapy in this extremely high-risk indication after failure of 2 or more prior lines of therapy [71, 72].

10.5 Testicular Lymphomas

Primary testicular lymphoma (PTL) accounts for less than 5% of all testicular tumors and only 1–2% of all non-Hodgkin lymphomas. The vast majority of cases (approximately 90%) are DLBCL, though rarely other histologies can involve the testis, including extranodal marginal zone lymphoma, BL, MCL, extranodal NK/T--cell lymphoma, peripheral T-cell lymphoma, and ALCL. This chapter will focus on primary DLBCL of the testis. PTL occurs at a median age in the late 60s and is the most common testicular malignancy in men over the age of 60 [73, 74]. The most common clinical presentation is with a painless unilateral testicular mass, and systemic "B" symptoms are uncommon. Three quarters of patients present with limited (Ann Arbor stages I–II) disease, with the remaining quarter presenting at advanced stage. Stage I patients have isolated testicular involvement, while stage II patients will also have involvement of the retroperitoneal nodes. Similar to PMBCL, when PTL presents at advanced stage, it has a predilection for extranodal locations, particularly the CNS and the contralateral testis. These sites are also common locations of relapse after initial therapy, with nearly a third of relapses involving the CNS [74, 75], most commonly the brain parenchyma. Interestingly, relapses in the CNS may occur as late as 10 years after initial treatment.

Diagnosis of PTL is typically made via orchiectomy. The tumor cells express pan B-cell markers CD19, CD20, and CD79A and are usually positive for BCL-2. Cell of origin, as determined either by gene expression profiling or immunohistochemistry, is the activated B-cell (ABC) subtype in the vast majority of cases. Activating MYD88 mutations are found in 70–86% of cases, often in association with a concomitant activating CD79B mutation [76, 77]. Deletions of the HLA loci are common, as are gains of chromosome 19q13 [78]. Copy number gains of 9p24.1, resulting in increased expression of PD-L1 and PD-L2, are also observed in the majority of cases and may have therapeutic relevance [77].

All patients with PTL require systemic therapy as the relapse rate after orchiectomy alone is approximately 80% with a median overall survival of 1 year [74, 75]. In a multicenter retrospective analysis of PTL by the International Extranodal Lymphoma Study Group (IELSG), the 5-year

overall survival for the entire population was 48%, but patients treated with combination chemotherapy (prior to rituximab), intrathecal chemotherapy, and prophylactic scrotal radiation had the best outcome with a 3-year overall survival of 88%. This led to a phase II clinical trial by the IELSG-evaluating R-CHOP, intrathecal methotrexate, and prophylactic scrotal radiation in 53 patients with limited-stage PTL and resulted in a 5-year PFS and OS of 74% and 85%, respectively [79]. This study did have three CNS relapses, one of which was in the brain parenchyma. Whether intrathecal methotrexate represents the optimal method of CNS prophylaxis, however, remains unknown. The majority of CNS recurrences of PTL occur within the brain parenchyma, which is unlikely to be successfully reached by intrathecal therapy alone. Further, intrathecal injections via lumbar puncture yield highly variable concentrations within the cerebral ventricles, with many patients not achieving therapeutic concentrations [80]. This has led some to employ systemic methotrexate for CNS prophylaxis in patients at high risk for CNS relapse of DLBCL, as it can be safely and effectively combined with R-CHOP, usually administered at a dose of 3–3.5 g/m^2 on day 15 of the 21-day R-CHOP cycle [81]. Whether systemic or intrathecal prophylaxis is preferable remains uncertain at this time, and so either modality can be considered appropriate. Certainly, optimal initial therapy of PTL should include orchiectomy, R-CHOP with incorporation of CNS prophylaxis (either intrathecal or systemic), and prophylactic scrotal radiotherapy.

Relapsed PTL is treated similar to other cases of relapsed DLBCL where second-line chemotherapy followed by high-dose chemotherapy with autologous stem cell transplant remains the treatment of choice for transplant-eligible patients with chemosensitive relapsed disease. Several biologically targeted therapies are also commercially available with biologic and clinical rationale in relapsed PTL. Both lenalidomide and ibrutinib have shown activity in relapsed DLBCL, particularly the ABC subtype which comprises most cases of PTL [82, 83]. Ibrutinib appears to have particularly encouraging activity within ABC DLBCLs which harbor mutations of both MYD88 and CD79B, a mutational pattern enriched within PTL, making this a potentially appealing therapy for chemorefractory disease. Amplification and expression of PD-1 ligands in the majority of PTLs also raise the prospect of PD-1/PD-L1 inhibitors in this disease, and preliminary evidence of efficacy has been demonstrated in a small number of patients [84]. Encouragingly, lenalidomide, ibrutinib, and PD-1 inhibitors have all shown activity in CNS lymphomas, which is of great relevance in this DLBCL subtype. Further data regarding the proper use and sequencing of these novel agents is needed.

10.6 Breast Lymphoma

Lymphomas localized to the breast represent about 2% of extranodal lymphomas and less than 1% of breast malignancies [85, 86]. DLBCL is the most frequent aggressive histology, although other types, including BL, may be seen. Of note, indolent lymphomas, particularly MALT, often appear in the breast and are managed akin to other localized indolent lymphomas. Primary breast DLBCL is biologically different from other sites. The mutational profile mostly involves the NF-kB signaling pathway, with a high frequency of *PIM1* mutations [87].

Primary breast lymphoma typically presents with a mass that is clinically suspicious of a breast carcinoma [88–90]. Local symptoms are frequent, whereas general manifestations are rare in localized cases. Surgical or core needle biopsy is mandatory for diagnosis as fine needle aspiration is insufficiently diagnostic. According to the largest retrospective study by the IELSG [90], primary DLBCL of the breast has some substantial differences with respect to standard nodal DLBCLs including (1) high risk of contralateral breast involvement, (2) relapse tendency in other extranodal sites, and (3) risk of CNS involvement or relapse (although this latter point remains controversial in the modern era). Based on the IELSG data, treatment with CHOP and radiation produced a median PFS and OS of 5.5 and 8 years,

respectively, in the pre-rituximab era. More recent data suggest that IF-RT still adds significant therapeutic benefits receiving chemoimmunotherapy [91]. Although not demonstrated in a specific trial, the addition of rituximab is likely to be beneficial, so R-CHOP is the current standard of care [9]. Whether increased CNS risk persists in the rituximab era is unclear as it has not emerged as a discrete risk factor on multivariable analyses in DLBCL. Attention should be paid to other risk factors, and CNS prophylaxis considered in patients with high-risk IPI scores, but insufficient data exists to recommend routine inclusion in low-risk patients with stage IE disease treated with combined modality therapy. Breast involvement in Burkitt lymphoma is common and should be managed similar to other Burkitt lymphomas with intensive regimens that include CNS prophylaxis.

10.7 Primary Cutaneous Lymphoma

The skin is a common site of lymphoma involvement, most frequently of T-cell origin (about 80%), including mycosis fungoides and primary cutaneous anaplastic large-cell lymphoma, usually presenting at early stage and managed by dermatologists. Among cutaneous B-cell lymphomas, most are indolent histologies such as MALT and primary cutaneous follicle center lymphomas, but a small percentage are DLBCL. Among the latter, primary cutaneous DLBCL leg-type is an aggressive lymphoma frequently seen in elderly women and appearing on the legs as the name implies. These lymphomas are of ABC origin and are characterized by an aggressive clinical course with subsequent relapse in extra-cutaneous sites in more than 50% of cases [92]. The outcome is generally unfavorable, with 5-year OS of about 50%. Treatment is with standard R-CHOP [93, 94], but novel approaches targeting the ABC subtype, such as with the inclusion of lenalidomide or ibrutinib, warrant investigation. The role of IF-RT is not well established, but given the relatively poor outcome with immunochemotherapy alone, radiation consolidation should be strongly considered for limited-stage disease.

10.8 Extranodal Aggressive Lymphoma in Other Locations

Aggressive extranodal lymphomas can arise in virtually any other extranodal site, but there is no sufficient data to classify them presently as discrete diseases with unique management recommendations. So DLBCLs occurring primarily within the lung, liver, kidney, adrenal gland, ovary, uterus, or other extranodal locations are typically treated with R-CHOP as with typical cases of DLBCL [24, 30]. Consolidative radiation therapy is not routinely employed in most visceral DLBCLs given the concern for organ toxicity, and the encouraging efficacy of R-CHOP alone, but should be considered on a case-by-case basis dependent on location, field size, and response to chemoimmunotherapy. Whether these discrete locations are independently associated with risk of CNS relapse remains controversial without consistent results observed in multivariable analyses in the modern era. Involvement of the kidney or adrenal gland has been fairly consistent and should warrant CNS prophylaxis in eligible patients [95]. Other extranodal locations should be assessed in the context of their overall disease burden and additional risk factors for CNS dissemination such as IPI score and translocation status of *MYC* and *BCL2* [96].

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