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Primary extranodal lymphoma of the glands. Literature review and options for best practice in 2019

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ABSTRACT

Primary extranodal non-Hodgkin's lymphomas (EN-NHL) are a heterogeneous group of malignancies that involve numerous entities with significant difference in terms of tumor site locations, prognostic factors, biology expression, and therapeutic options. In the literature, many EN-NHL types were reported from limited series which only allowed narrow views for elucidating prognostic factors and defining the role of loco-regional therapies in the era of new systemic and biologically targeted therapies. The *Rare Cancer Network (RCN)*, an international multidisciplinary consortium, has published a number of reports on several EN-NHL sites which included many gland locations. In this review, we will focus on the recent literature for a selected number of EN-NHL types in both exocrine and endocrine gland locations. We aim to provide renewed and clear messages for the best practice in 2019 for diagnosis, histopathology, treatments, and also their prognostic implications. We believe that better understanding of molecular and genetic characteristics of these particular diseases is crucial for an appropriate management in the era of personalized treatment developments.

1. Introduction

Primary extranodal non-Hodgkin's lymphoma (EN-NHL) is a heterogeneous group of diseases involving numerous entities, with significant differences in terms of tumor site, natural history, and therapeutic options as compared to nodal non-Hodgkin's lymphoma (NHL). Primary EN-NHL of glands is rare and often are subjects of clinical and academic debate in terms of diagnosis, since glands may be the sanctuary sites of secondary involvement or metastasis from another primary malignancy that is organ-based. A general definition of all EN-NHL of glands does not exist. To facilitate this research, we here consider primary EN-NHL of glands as a histologically proven lymphoma of a homogeneous organ and fulfills the following criteria: (1) there is no history of lymphoma or carcinoma elsewhere; (2) there is no known dissemination in peripheral blood and bone marrow; (3) if lymph nodes and other organs are involved, lesions of the gland are unequivocally dominant (Fox et al., 1988; Jeanneret-Sozzi et al., 2008; Lei, 1998; Ansell et al., 1999; Salvatore et al., 2000; Rashidi and Fisher, 2013). To our best knowledge, primary glandular NHL have never been reported or summarized in a systematic review before.

In this review, we aim to report the current landscape for diagnoses according to each glandular location of NHL, and provide modern therapeutic options including the relevant literature and *Rare Cancer Network* (RCN) experiences, wherever applicable. Finally, we also conclude each chapter by highlighting “best practice” for diagnosis and therapy.

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2. Methods

To conduct this review, a comprehensive literature search was performed using the MEDLINE database for EN-NHL of each glandular site; if specific sites were reported by RCN, the search also included after the dates of publication which were between 1993 and 2017. We reviewed all reports from the RCN and summarized the results regarding their recommended treatment strategies. We then collected the more recent publications using the MEDLINE search results of other studies and clinical trials, and provided additional reviews for each of the EN-NHL sites. First, general key words for treatment of EN-NHL including "lymphoma and radiotherapy", "lymphoma AND chemotherapy", "lymphoma and surgery", "immunotherapy AND lymphoma AND radiotherapy", and "rituximab AND lymphoma AND CHOP" were used. In the second step, we used specific key words as relevant to the endocrine and exocrine NHL disease sites.

Only reports written in English were reviewed. Regarding the rarity of these diseases, all study types (case reports, case series, clinical trials, and retrospective reviews), regardless of sample size, were considered for this review.

3. Results

3.1. Endocrine glands

"Endocrine glands" are glands of endocrine system that secret their products directly into the blood stream. The major glands of the endocrine system include the pineal gland, pituitary gland, hypothalamus, thyroid, adrenal glands, ovaries, and testes. Primary lymphoma of thymic and parathyroid glands were excluded from this review. Thymic NHL is not traditionally considered as an EN-NHL. There are no known published reports regarding parathyroid glands. Altogether, only about 3% of NHL arise primarily in an endocrine organ (Zucca, 2008).

3.1.1. Lymphomas of pure endocrine glands

3.1.1.1. Primary thyroid lymphoma

3.1.1.1.1. Epidemiology. Primary thyroid lymphoma (PTL) is a rare disease, accounting for 2–5% of thyroid malignancies and 3–7% of EN-NHLs; however, it is the most common endocrine organ in which primary NHL may arise (Ansell et al., 1999; Green et al., 2006). PTL presents in the seventh decade with a female predominance, with a 3:1 ratio compared to male (Pedersen and Pedersen, 1996; Ansell et al., 1999). Among patients with Hashimoto's thyroiditis, the risk of PTL are 40–80 times higher than in patients without thyroiditis (Pedersen and Pedersen, 1996).

3.1.1.1.2. Diagnosis. The major symptom presenting in more than 90% of the PTL patients is a rapidly enlarging, painless goiter with cervical lymphadenopathy and symptoms of organ compression. There are no biochemical abnormalities specific to PTL (Thieblemont et al., 2002). The diagnosis of PTL is established by histopathologic examination through biopsy specimens. Serum anti-microsomal and anti-thyroglobulin antibodies are elevated in 95% of the PTL patients (Gupta et al., 2005). Circulating antibodies to thyroid peroxidase is also positive in patients with Hashimoto's thyroiditis (Sakorafas et al., 2010).

Fluorine-18-fluorodeoxyglucose positron emission tomography combined with X-ray computed tomography scan (^{18}FDG-PET-CT or PET-CT) can be useful in staging, restaging, or assessing treatment response (Treglia et al., 2013).

PTL is almost of B-cell lineage, but occasional patients with Hodgkin's and T-cell lymphomas were reported (Pedersen and Pedersen, 1996). Up to 70% of PTL are diffuse large B-cell lymphoma (DLBCL), and mucosa-associated lymphoid tissue (MALT) lymphoma accounts for the majority of the remaining 30% which are generally associated with Hashimoto's thyroiditis (Graff-Baker et al., 2009). Reported molecular abnormalities included a loss of expression of B-cell lymphoma (Bcl-2) and an increase in p53 inactivation in higher grade disease (Graff-Baker et al., 2010).

3.1.1.1.3. Treatment. The principle of combining chemotherapy (CXT) and radiation therapy (RT) in aggressive lymphoma is to reduce both the risks of distant and locoregional recurrence (LRR), resulting in better outcomes compared to a single modality. In historical series, excellent survival with nearly 100% rate was reported at 8 years for patients treated with CHOP-based CXT and local RT (Matsuzuka et al., 1993). Ha et al. reported 5-year failure-free survival (FFS) rates for patients treated with surgery plus RT, CXT alone, and combined RT-CXT being 76%, 50%, and 91%, respectively ($p = 0.15$) (Ha et al., 2001). Rituximab has been effective with CHOP regimen in elderly patients with DLBCL-type PTL (Jonak et al., 2010).

Definitive external beam radiotherapy (EBRT) at moderate dose may be an appropriate choice for MALT lymphoma of thyroid, with excellent outcome (Tsang et al., 2003). The *RCN* series (Onal et al., 2011) published in 2011 represented one of the largest series with 87 patients treated for localized PTL. Patients had RT, CXT with or without diagnostic surgery, or combined RT and CXT (CMT). The long-term outcome was excellent, and comparable to other series with 10-year overall (OS) and disease-free survival (DFS) rates being 71% and 64%, respectively. Higher RT dose $\geq$40 Gy improves local control (Anacak et al., 2012) rates compared with lower RT doses (94 vs. 78%, p = 0.04). Independent factors influencing outcomes include age, B-symptoms, lymph node involvement, and treatment modality. High-grade histology, lack of RT, advanced stage, mediastinal involvement, rapid-growth tumors, etc. were also factors for poor prognosis (Tsang et al., 2003; Graff-Baker et al., 2009).

3.1.1.1.4. Conclusion and best practice. The diagnostic work-up should include a complete medical history and physical examination and a comprehensive pathological review of the thyroid or nodal specimen. PTL staging consists of cervical ultrasound (US) and cervico-thoracic computed tomography (CT)-scan. PET-CT is recommended for aggressive histologies. Surgery other than for diagnostic purposes should be omitted. Standard of care for PTL are CMT with anthracycline-based CXT, and involved-field RT (IFRT) of $\geq$40 Gy to the entire thyroid and involve lymph nodes; rituximab should be considered for the DLBCL subtype. EBRT alone may be an appropriate choice for MALT subtype.

3.1.1.2. Primary lymphoma of adrenal gland

3.1.1.2.1. Epidemiology. Primary adrenal lymphoma (PAL) is rare and represents < 0.2% of EN-NHL; less than 200 cases have been reported in the literature (Rashidi and Fisher, 2013). Conversely, involvement of adrenal glands by NHL is not uncommon, rising up to 42% in autopsy case series (Straus et al., 1983). PAL has a tendency to involve elderly males in their sixth decade of life. Asian populations seem to be most commonly affected (54% of cases) (Rashidi and Fisher, 2013). The exact pathogenesis of PAL remains unknown; however, multiple factors have been reported including immune dysfunction, EBV infection, and mutation in p53 and c-kit genes (Nakatsuka et al., 2002).

3.1.1.2.2. Diagnosis. PAL is a highly aggressive subtype of EN-NHL which presents frequently with constitutional B-symptoms, abdominal pain, fatigue, and adrenal insufficiency (Grigg and Connors, 2003). This can be interpreted as a consequence of high burden tumors, with median size of 8 cm and bilateral involvement commonly presented in 75% of patients (Rashidi and Fisher, 2013). On imaging, PAL is a metabolically hyperactive, hypovascular tumor.

Definitive diagnosis is obtained only by tissue biopsy, mostly via needle core biopsy after excluding catecholamine excess states. Almost PALs are high grade (95%), with DLBCL being the most common subtype; T-cell lymphomas can also be seen in < 10% of cases (Grigg and Connors, 2003; Rashidi and Fisher, 2013). About 18% of the cases are disseminated at presentation. BM invasion can be seen in 6% of cases. CNS involvement can occur synchronously or metachronously in 18%

of the PAL cases, and carries a negative impact on long-term prognosis (Grigg and Connors, 2003).

3.1.1.2.3. Treatment. PAL has a poor prognosis. While a good initial response after CXT could be obtained, durable remission is rare (Grigg and Connors, 2003). Historically, the median survival was shown to be between 3 and 12 months. The largest series on 31 PA L in Korean patients showed that outcomes with R − CHOP were much better than those previously reported (Kim et al., 2012). The 2-year OS and PFS were 68.3% and 51.1%, respectively. CNS relapse rate was high at 13% despite a good initial response, suggesting a possible role of CNS prophylaxis in PAL. As the normal adrenal function and tissues should be preserved for as much as possible, surgery and RT are somewhat discouraged in the management of PAL as a result.

3.1.1.2.4. Conclusion and best practice. Definitive diagnosis is required by adrenal biopsy after excluding catecholamine excess states. CNS evaluation is preferred as part of the complete staging, along with PET-CT and BM biopsy. Therapeutic option including CXT with R − CHOP is preferred. CNS prophylaxis should be considered in high-risk patient cases. The roles of surgery and RT need further evaluation, and are typically not indicated currently.

3.1.2. Lymphomas of sexual endocrine glands

3.1.2.1. Primary testicular lymphoma

3.1.2.1.1. Epidemiology. Primary testicular lymphoma (PTsL) is an uncommon and aggressive form of EN-NHL accounting for 1% of NHL and < 5% of all testicular malignancies (Gundrum et al., 2009). Median age at diagnosis is 67 years. PTsL is both the most common testicular malignancy in men older than 60 years and the most common bilateral testicular neoplasm (Vitolo et al., 2011). Human immunodeficiency virus (HIV) infection is a known risk factor for aggressive NHL, of which patients are commonly younger and have a very poor OS (less than 6 months usually) (Knowles, 2003).

3.1.2.1.2. Diagnosis. In 30–40% of the cases, typical presentation consists of a unilateral painless testicular mass or hydrocele. Synchronous bilateral involvement occurs in 6–10% of all cases (Vitolo et al., 2008). Systemic B symptoms are present in 25–41% of patients with advanced stages (Vitolo et al., 2008). At relapse, PTsL tends to involve EN organs including the central nervous system (CNS), skin, contralateral testis, and pleura (Gundrum et al., 2009).

PTsL appears on US with areas of hypoechogenicity with hypervascularity in an enlarged testis. On magnetic resonance imaging (MRI), PTsL is characterized by T2 hypointense and heterogeneous gadolinium enhancement (Srisuwan et al., 2011). The diagnosis of PTsL is surgically established by inguinal orchiectomy for adequate pathologic specimen.

Similar to other aggressive forms of NHL, staging evaluation consists of a complete physical examination (with thorough evaluation of the skin) and laboratory test (with HIV serology), PET-CT, bone marrow (BM) biopsy with the addition of specific CNS staging by lumbar puncture (LP) for cerebrospinal fluid (CSF) analysis, and a brain MRI (Bertolotto et al., 2014; Cheson et al., 2014).

The majority of PTsL (65–90%) are DLBCLs, although patients with HIV infection may present with more aggressive variants. DLBCL PTsLs typically express B-cell markers cluster of differentiation (CD19, CD20, CD79a, and PAX5); Bcl-2 protein is expressed in 70% of cases but Bcl-6 is rarely positive. Rare histologies include mantle cell lymphoma, EN-NK-cell lymphoma, and peripheral T-cell lymphoma which are associated with worse prognoses (Haroon and Ahmed, 2013; Ambrosio et al., 2014).

3.1.2.1.3. Treatment. Orchiectomy alone used to be indicated for both diagnostic and therapeutic purposes, as often the blood-testis barrier makes the testes an isolated sanctuary site for systemic therapies. However, the outcomes of patients treated with orchiectomy and/or RT were poor (Gundrum et al., 2009). Since then, the outcome of PTsL patients has been gradually improving with the addition of CHOP-based CXT, achieving 5-year OS rates of 30–52% (Zouhair et al., 2002; Gundrum et al., 2009). Patients who received more than 6 cycles of CXT had a better long-term outcome than those who were treated for a shorter period (10-year OS, 44% vs. 19%, $p = 0.03$) (Zucca et al., 2003). A recent Canadian retrospective analysis of 134 PTsL patients treated with CHOP with (n = 61) or without (n = 73) rituximab found in an impact of rituximab on progression-free survival (PFS) (hazard ratio (HR) 0.42, $p < 0.001$) and OS (HR 0.39, $p < 0.001$). Rituximab did not seem to improve outcome for patients who had CNS relapse in this study (Kridel et al., 2017).

RT alone for PTsL should be avoided unless patients refuse or are unfit for systemic CXT. Patients treated by orchiectomy and anthracycline-based CXT had an increased risk of controlateral testis relapse, as high as 45% in the absence of scrotal irradiation in the IELSG series (Zucca et al., 2003). In a subsequent IELSG-10 study, all patients received adjuvant contralateral testicular RT (30 Gy), and none had testicular relapses (Vitolo et al., 2011). Involved-field RT to para-aortic and pelvic nodes was indicated in 9 patients with stage II disease (30–35 Gy in patients with complete remission [CR], 35–45 Gy for those with unconfirmed CR [CRu] or progressive disease [PD] at the end of CXT with only one site of in-field relapse) (Vitolo et al., 2011). Despite this, the SEER data showed that RT was underutilized (Gundrum et al., 2009).

In an attempt to decrease risk of CNS relapse, intrathecal (ITC) CXT has been used in many retrospective series (Mazloom et al., 2010). Prospective clinical trials (Vitolo et al., 2011) used ITC CXT and reported low CNS relapse rates of 0–6% which were significantly better compared to historical controls. Another approach was to combine high-dose systemic methotrexate (MTX) to ITC CXT for CNS prophylaxis as it could achieve higher drug penetration into the brain parenchyma (Balis et al., 2000). This approach appeared to lower the risk of CNS relapse (Holte et al., 2013) and is currently being investigated in the ongoing IELSG-30 phase 2 trial (*NCT00945724*, ClinicalTrials.gov).

In the pre-rituximab era, the *RCN* published a series of 36 patients with PTsL (Zouhair et al., 2002). Orchiectomy was performed in all but one patient. RT was delivered to 61% of the cases with a median dose of 31 Gy, CXT was administered in almost all of the patients (81%), and ITC MTX was used in 7 patients. Five-year OS and DFS rates were 47% and 43%, respectively. Despite CNS prophylaxis, CNS relapse rate remained high (22%).

The IELSG-10 study (Vitolo et al., 2011) was a multicenter phase 2 trial of 53 early-stage PTsL patients. They evaluated the use of R − CHOP followed by locoregional RT, ITC MTX was used for CNS prophylaxis. After median follow-up of 65 months, the 5-year PFS and OS rates were 74% and 85%, respectively. CNS relapse was reported in 6% of the cases. The excellent results in this study established R − CHOP every 21 days with ITC MTX and locoregional RT as the standard of care for patients with limited-staged PTsL.

The International Prognostic Index (IPI) score and its components are good surrogate markers of high burden tumor and disseminated disease but have a limited utility in limited stage because of its typically lower scoring. CMT with locoregional RT covering the contralateral testis and anthracyclin-based CXT improved both DFS and OS (Zouhair et al., 2002; Zucca et al., 2003). Infiltration of adjacent tissues were associated with a worse prognosis (Wang et al., 2013).

3.1.2.1.4. Conclusion and best practice. As with other aggressive NHLs, similar staging methods are recommended for PTsL (PET-CT, BM aspiration), with addition of CNS staging (PL for CSF examination, brain MRI). High inguinal orchiectomy is performed for both diagnostic and therapeutic purposes. Current international standard of care for localized, well-fit PTsL patients consists of 6 cycles or more of R − CHOP with ITC MTX followed by locoregional RT.

3.1.2.2. Primary ovarian lymphoma

3.1.2.2.1. Epidemiology. Ovarian involvement by malignant lymphoma is well recognized and can be seen in 7–26% of cases in

autopsy series. Primary ovarian lymphomas (POL), however, are rare, and account for only 0.5% of NHL and 1.5% of all ovarian neoplasms (Nasioudis et al., 2017). When stringent criteria of Fox and Paladugu were adopted (Fox et al., 1988), acceptable reported POL cases did not exceed 50 patients in recent years (Zhao et al., 2011). Patients diagnosed with POL have had a mean age of 45 years (range, 6–74 years) (Yun et al., 2010; Zhao et al., 2011).

3.1.2.2.2. Diagnosis. Presentation of POL is similar to ovarian carcinomas, with abdominal pain, large pelvic mass and ascites. B-symptoms are noted in 10–33% of patients. Most of the ovarian carcinomas have elevated serum levels of CA-125, however, it is not specific and can also be elevated in POL. If it does elevate in POL, it is a very sensitive marker for surveillance. Radiological appearances do not seem to differ much from those of ovarian carcinomas, making histological sampling is mandatory for diagnosis. PET-CT is helpful in initial evaluation, staging, and follow-up of POL patients, as in other high-grade NHL cases. The majority of POL's are B-cell in origin (80–95%), and DLBCL is the most common histological subtype. Bilateral involvement was seen in 36–71% of the cases (Yun et al., 2010; Nasioudis et al., 2017).

3.1.2.2.3. Treatment. POL has a poor outcome, with 3-year OS of 0–36% in series. IPI score is a significant prognostic factor for survival in POL patients. Due to the rarity of POL, there are no published guidelines for therapeutic management. Surgery is often performed as primary evaluation, despite the fact that it typically does not improve survival. POL was traditionally thought to be an EN-NHL with dismal prognoses, however, recent studies with R − CHOP demonstrated similar outcomes to that of nodal DLBCL (Yun et al., 2010). RT is not preferred due to high risks of recurrent disease outside the RT field, abdominal toxicities, and potential loss of fertility in younger patients, but can be considered on an individual basis. When given, RT doses are typically in the range of 30–36 Gy. CNS is the most common site of relapse, occurring in 23–40% of patients. CNS prophylaxis is strongly considered in high-risk patients, with 4–8 doses of ITC MTX or cytarabine (Yadav et al., 2014).

3.1.2.2.4. Conclusion and best practice. If possible, diagnosis should be established with biopsy rather than surgical resection. Staging for POL needs to include CNS examination, along with other biological and radiological testing as for other high-grade EN-NHL cases. Treatments should consist of CXT with R − CHOP and also CNS prophylaxis. Surgery should be limited for treatment complications only, such as bowel obstruction or bleeding. RT should be considered on a case-by-case basis.

3.1.2.3. Primary prostatic lymphoma

3.1.2.3.1. Epidemiology. Primary prostatic lymphoma (PPrL) accounts for 0.09% of all prostate neoplasms and 0.1% of all NHL cases (Terris et al., 1997; Bostwick et al., 1998). A larger proportion of secondary prostatic involvements, as in NHL cases of ovaries, was described (Bostwick et al., 1998). When the stringent criteria for PPrL of Bostwick et al., were applied (Bostwick et al., 1998), the number of cases reported in the literature have not exceeded more than 100 patients. PPrL appears principally in elderly men in their sixth decade. Unlike other EN-NHL, no presumable causality of PPrL is established.

3.1.2.3.2. Diagnosis. Clinical presentations of PPrL usually mimic lower urinary tract obstruction from other benign causes, such as benign prostatic hypertrophy or chronic prostatitis, causing a delay in treatment (Ezekwudo et al., 2017; Tamang et al., 2017). The level of serum PSA is typically not elevated (Bostwick et al., 1998; Tamang et al., 2017). On imaging, PPrL appears as a hypermetabolic enlarged prostate, with or without invasion of seminal vesicles (Kakkar et al., 2015; Ezekwudo et al., 2017). PET-CT is helpful in then staging of PPrL, as more than 70% of cases develop lymphomatous dissemination within 1–59 months from diagnosis (Bostwick et al., 1998). PPrL is very heterogeneous in term of histologic subtypes, with the most common subtype being DLBCL (Bostwick et al., 1998; Manabe et al., 2012). IHC staining of PPrL is positive for CD45 and CD20, and negative for PSA and pancytokeratin which differ from those of prostatic adenocarcinoma.

3.1.2.3.3. Treatment. Due to its extreme rarity, no clear guidelines to the management of PPrL could be established. The treatment modalities included surgery, CXT and/or RT (Terris et al., 1997; Bostwick et al., 1998; Manabe et al., 2012). While Bostwick et al. did not find any difference in lymphoma-specific and overall survivals among all sub-groups regardless of origin (primary or secondary NHL of the prostate), histologic subtypes and therapeutic modalities (Bostwick et al., 1998), a separate Japanese study with 19 localized PPrL patients demonstrated a clear benefit of systemic CXT over other prostate-directed treatments (Manabe et al., 2012). Recent data have shown better outcomes with combined CXT (R − CHOP), making this the mainstay of therapy in the modern era.

3.1.2.3.4. Conclusion. Despite its rarity, PPrL should be considered as differential diagnosis in patients with obstructive urinary symptoms who present with normal PSA levels. PET-CT is highly recommended due to its high incidence of distant metastases. Systemic CXT is preferred over local treatments, with R − CHOP being the standard of care.

3.1.3. Other rare lymphomas of endocrine glands

Other EN-NHL types of endocrine glands, principally located in the central nervous system (CNS), are extremely rare. They are reported only in case reports and limited patient series.

3.1.3.1. Primary lymphoma of endocrine glands in the central nervous system. Primary central nervous system lymphoma (PCNSL) is rare, accounting for 2–3% of all NHL cases, and approximately 4% of primary brain tumors (Ferreri et al., 2003; Rubenstein et al., 2008). EN-NHLs of the glands in the CNS are even more uncommon, with only a few case reports in the literature. In general, they share the same characteristics as other PCNSL in term of epidemiology, radiologic presentations, and management. Otherwise, clinical presentations may differ depending on endocrine function of the affected gland.

3.1.3.1.1. Primary lymphoma of pineal gland (PPinL). PCNSL arising in the pineal gland is particularly rare, and has only been reported in eight references in the literature (Gupta et al., 2015). The average age at diagnosis of PPinL was in the sixth decade, and only one female patient aged 72 years was reported (Pantanowitz et al., 2003). Aggressive B-cell lymphoma has been the most common histologic subtype including DLBCL, malignant B-cell lymphoma, immunoblastic lymphoma, and anaplastic large cell lymphoma (Yoshida et al., 2014; Gupta et al., 2015). Radiological appearance is not specific. A histologic diagnosis is essential prior to initiating treatment, especially in the modern era with molecular therapy options (Yoshida et al., 2014).

There is no consensus of treatment due to its extreme rarity. Almost all patients were treated with CXT (Amagasa et al., 1996; Karikari et al., 2007), with 2 cases treated with RT to the tumor site, and 1 received hematopoietic stem cell transplantation after the first CR with CXT (Yoshida et al., 2014). No resection was being attempted, perhaps due to its complexity and the organ location being fairly deep in the brain.

3.1.3.1.2. Primary lymphoma of pituitary gland (PPitL). Primary pituitary lymphoma (PPitL) is a rare entity of pituitary neoplastic diseases; there were only fewer than 30 reported cases of PPitL throughout the literature, and the majority of cases were summarized in the last 10 years (Rainsbury et al., 2012). The gender distribution of PPitL and age at diagnosis seem to be similar to those of other PCNSL cases (Giustina et al., 2001).

Clinical presentation includes hypopituitarism associated with diabetes insipidus, headache, visual field defects, and even cranial nerve palsies. The majority of cases (65%) had an aggressive histology similar to B-cell lymphomas (Rainsbury et al., 2012), and only one patient presented a low grade subtype of lymphoplasmacytic lymphoma, an extremely rare variant that constitutes 3% of all PCNSL cases (Carrasco

et al., 2012).

Therapeutic options include RT, CXT or CMT. It was very challenging to estimate survival rates from the literature due to limited follow-up, but we can estimate that approximately 60% of patients had survivals of more than 6 months, and about 13% of patients lived between 12–14 months (Giustina et al., 2001; Carrasco et al., 2012).

3.1.3.1.3. Primary lymphoma of hypothalamus. Hypothalamus is anatomically and functionally closely related to the pituitary gland, making it the "command center" of the neuroendocrine system. However, primary EN-NHL presents at this location is less frequent than that in the pituitary gland. Hypothalamic involvement in the context of leptomeningeal dissemination in PCNSL was reported occasionally, however, solitary hypothalamic lesions were only reported in fewer than 10 cases in the literature (Bhatti et al., 2005; Layden et al., 2011). Most of cases are males, and age 50 years old on average.

Clinical presentation reveals perisellar localization with diabetes insipidus or visual perturbation. On brain MRI, a single hypothalamic lesion was found which was homogenously enhanced after gadolinium intravenous injection. Histopathological diagnosis was obtained by biopsy; the majority of cases were DLBCL CD20+ (Bhatti et al., 2005; Layden et al., 2011).

Treatment details were not reported in most cases. According to available information, patients were treated similar to other PCNSL cases, including high dose MTX-based CXT with or without WBRT. Outcomes from only two patients were reported, both without evidence of recurrence at 6 months of follow-up (Park et al., 2007; Layden et al., 2011).

Conclusion and best practice

The pretreatment evaluation of EN-NHL patients with primary CNS gland involvement should incorporate some additional exams (compared to non-CNS aggressive NHL cases), including ophthalmologic examination, LP, brain MRI, and evaluation of cognitive function for therapeutic decision-making. Aside from the cornerstone high-dose systemic MTX, there is really little consensus on the optimal components or sequences of treatments for these extremely rare entities. Whenever feasible, rituximab is suggested for improving patient outcomes. Despite the radiosensitive nature of PCNSL, utility of EBRT as consolidation therapy should be carefully considered, weighing its benefit and risk ratio against the potentials of neurocognitive dysfunction.

3.2. Exocrine glands

Exocrine glands are glands that produce and secrete substances onto an epithelial surface by way of a duct. They include sweat, salivary, mammary, lacrimal, sebaceous, and mucous glands. Cutaneous adnexal gland lymphoma is identified as secondary lymphocytic infiltration of cutaneous T-cell lymphoma variants, such as Mycosis Fungoides and Sézary syndrome, and are excluded from the discussions here.

3.2.1. Primary lymphoma of the salivary glands

3.2.1.1. Epidemiology. NHL of the salivary glands (SGL) is a rare disease, representing 1.7% of salivary gland malignancies. SGL may develop as a primary tumor, or as a result of a disseminated disease in salivary glands in less than 10% of NHLs (Tagnon et al., 2002). Parotid glands are the most commonly involved site, followed by submandibular and sublingual glands; involvement of the minor salivary glands is occasionally reported. SGL presents mostly in patients of 55–65 years old, and with a female predominance (Vazquez et al., 2015). Sjögren's Syndrome (SS), a chronic autoimmune disorder affecting exocrine glands, is a well-known risk factor of developing MALT-type SGL. The risk was reported as 44 times higher in patients with SS compared to the general population, with a latency period of several years (Smedby et al., 2006); HCV infection might also be implicated (Arcaini et al., 2012).

3.2.1.2. Diagnosis. Most of patients with SGL show a progressively enlarging, unilateral, painless mass associated with enlarged cervical lymph nodes. Due to its connection to autoimmune disorder, all salivary glands in the same patient are at risk of developing SGL synchronously or metachronously, and, as a result, they should all be carefully examined. The diagnosis of SGL is established by histopathologic examination of the affected salivary gland specimen(s) obtained by FNA or incisional biopsies. Almost SGL are of B-cell lineage including MALT, DLBCL, and FL (Smedby et al., 2006; Vazquez et al., 2015).

Considering the autoimmune background and high probability of cure with local therapies, it seems appropriate to categorize all salivary glands as a single extra-nodal organ and stage them as IE, IIE or IIIE accordingly, depending on the degree of nodal involvement (Mac Manus et al., 2007).

3.2.1.3. Treatment. EBRT has recently replaced surgery in the treatment of MALT lymphoma subtypes. Moderate RT dose (25–30 Gy) is a safe and effective strategy for early-stage MALT lymphoma, with local control (LC) rates around 90–97% (Tsang et al., 2001). A multicentric phase II study by the Japan Radiation Oncology Group evaluated the role of RT in extra-gastric MALT lymphoma. CR or CRu was achieved in 92%. The 3-year OS, PFS, and LC rates were 100%, 92%, and 97%, respectively (Isobe et al., 2007). Kalpadakis et al. reported 20 SGL cases among 76 patients with extra-gastric MALT lymphoma; cause-specific survival (CSS) was 94%, but PFS was only 56% at 5 years (Kalpadakis et al., 2008).

The multi-institutional *RCN* study retrospectively analyzed 62 cases of MALT SGL. Two third of patients were treated by RT, resulting in a longer DFS (Anacak et al., 2012). In the SEER database analysis (n = 172), Vazquez et al. did not find any difference in term of efficacy between surgery and RT, with long-term survival rates exceeding 80% equally (Vazquez et al., 2015). Another analysis of SEER database on EN MALT reported lymphoma-related deaths in 4.2% of SGL, and this rate rose to 8.4% when RT was not delivered (Olszewski and Desai, 2014).

The role of CXT is unclear in the management of SGL due to its indolent nature. In the ISELG-41 study, only 37 of 247 patients were treated with CXT initially, and 47% of those receiving rituximab. OS was better in patients with Sjögren's Syndrome, and in those who received rituximab (Jackson et al., 2015). Younger patients and lower IPI scores were also associated with better outcomes.

3.2.1.4. Conclusion and best practice. Any patient with a diagnosis of SGL should be evaluated for potential dissemination of the disease throughout all salivary glands. Surgery, especially parotidectomy, should be avoided. Monotherapy with local RT is effective as the first line treatment of MALT lymphoma. Systemic therapy including rituximab can be considered for disseminated or aggressive disease states.

3.2.2. Primary breast lymphoma

3.2.2.1. Epidemiology. Primary breast lymphoma (PBL) is rare, accounting for less than 0.5% of all breast malignancies and 1–2% of EN-NHLs. Conversely, secondary involvement of the breast with lymphomas is quite common. PBL demonstrates a bimodal age distribution, with incidence peaks in the fourth and seventh decades of life (Surov et al., 2012).

3.2.2.2. Diagnosis. The majority (60%) of PBL cases presents as a unilateral, painless breast mass in an older woman. Ipsilateral axillary adenopathy is present in 25% of cases (Jeanneret-Sozzi et al., 2008). Systemic B-symptoms are uncommon.

Most of lesions are oval-shaped (71%) and high-density (91%) single masses without speculated margins or calcifications in mammography (Lyou et al., 2007). On MRI, PBL lesions are characterized as T2 hyperintense and T1 isointense (Yang et al., 2007; Surov et al., 2012).

Using Lugano classification, staging procedures include a careful history and physical examination, appropriate imaging (PET-CT), BM aspiration and biopsy, and laboratory studies including serum LDH (Cheson et al., 2014). Assessment of the contralateral breast is essential since approximately 10% of cases are bilateral (Loughrey et al., 2004).

Almost all of PBLs are B-cell in lineage, and approximately one-half of them are DLBCL. Indolent histologies, i.e. FL or MALT, occur less commonly (Loughrey et al., 2004). T-cell lymphomas rarely arise in the breast, and are usually associated with an aggressive clinical course (Aguilera et al., 2000). Women with silicone breast implants have an increased risk of developing anaplastic large cell lymphoma (ALCL), of 18-fold higher, than women who do not have an implant (de Jong et al., 2008).

3.2.2.3. Treatment. In general, treatment of PBL follows guidelines for other EN-NHLs of the same stage and histology. Mastectomy does not appear to improve survival or risk of recurrence for most PBL subtypes. Higher relapse rate and poorer survival after radical surgery were noted especially in surgical reports without RT (Fruchart et al., 2005; Jeanneret-Sozzi et al., 2008; Avenia et al., 2010). A potential exception is breast implant-associated ALCL confined by the fibrous capsule surrounding the implant for which complete capsulectomy is appropriate and curative, and is considered first-line treatment of choice (Clemens et al., 2016).

RT plays a central role in the treatment of PBL. In the *RCN* study, RT to the breast or to the thoracic wall at 40 Gy in 20 fractions improved the 5-year LC rates significantly, compared to no RT at all (76–95%, $p = 0.02$) (Jeanneret-Sozzi et al., 2008). In the IELSG series, RT was delivered after surgery or biopsy with a median dose of 38 Gy, no LRR improvement was noted among patients receiving RT. The majority of recurrences occurred distantly, and only 8% in the contralateral breast (Martinelli et al., 2009).

CHOP or CHOP-like regimens were mostly associated with positive outcome (Kuper-Hommel et al., 2003). Aviles et al. published their randomized trial of PBL, in which 96 patients were allocated to RT (n = 30), CXT (n = 32), and CMT (n = 34). At 10 years, actuarial OS was 50%, 50% and 76%, respectively ($p < 0.01$) (Aviles et al., 2005). A positive impact of CMT +/- rituximab in PBL was also suggested in the more aggressive DLBCL subtype (Ou et al., 2014; Radkani et al., 2014).

The role of CNS prophylaxis in PBL is controversial. Case series have reported a high incidence of CNS recurrence at 5–17% or even higher if Burkitt's lymphoma was included (Ou et al., 2014; Ryan et al., 2008).

Prognosis is dependent on clinical stage and histologic subtype. Poor prognostic factors include age greater than 60 years, elevated serum LDH, more advanced stages, and PS 2 or worse. Breast conserving surgery, anthracycline-based CXT, and RT are associated with better outcomes (Martinelli et al., 2009; Ryan et al., 2008).

3.2.2.4. Conclusion and best practice. Ulrasaound and MRI of the breast should be used for evaluating tumor size and nodal involvement. PET-CT is considered for more appropriate staging in high-grade NHL. Total mastectomy is unnecessary and should be avoided, except for breast implant-associated ALCL where complete capsulectomy is appropriate and treatment of choice. RT plays a central role in PBL; RT is administered to the whole breast at a dose of 40 Gy in 20 fractions after biopsy or conservative surgery. CXT should contain anthracycline; rituximab can be considered for DLBCL subtype. Given the high incidence of CNS recurrence, CNS prophylaxis may be considered.

3.2.3. Primary orbital and lacrimal gland lymphomas

3.2.3.1. Epidemiology. Although rare, lymphomas are the most common malignancies of the orbit and lacrimal gland, but only accounted for < 1% of all EN-NHL cases (Coupland, 2004). A marked increase in incidence has been observed over the past few decades (Martinet et al., 2003). They most commonly affect older patients of fifth to seventh decade of age, with a female predominance (Ferry et al., 2007). Recently, Ferreri et al. demonstrated an association between ocular adnexal marginal zone lymphoma (OAMZL) and infection with *Chlamydia psittaci* (Cp) in Italian patients (Ferreri et al., 2012). However, several subsequent studies from different countries suggested variability across the sampled geographic regions (Husain et al., 2007).

3.2.3.2. Diagnosis. The presenting symptoms of primary lacrimal lymphoma (PLL) may include lacrimal gland enlargement, proptosis, eyelid swelling, and visual acuity changes (Stefanovic and Lossos, 2009). Bilateral gland involvement occurs in 10–17% of cases (80% simultaneous, 20% sequentially) (Ferry et al., 2007). The majority (60–90%) of patients present with localized disease (stage IE) (Martinet et al., 2003; Ferry et al., 2007).

The initial evaluation requires a careful ophthalmologic examination and adequate tumor sampling for histopathologic diagnosis. The approach for staging primary orbital lymphoma (PORL) and PLL is similar to that for other NHL types in general. CT-scan and MRI aid in the assessment of location, size, and degree of tumoral infiltration (Roe et al., 2006). PET-CT may have a higher sensitivity than CT-scan in detecting distant metastatic disease (Cheson et al., 2014).

Almost all PORLs and PLLs are low-grade B-cell lymphomas including MZL, FL, and small B-lymphocytic subtypes; high-grade DLBCL is most frequent. T-cell lymphomas are particularly rare, and Hodgkin's lymphoma is limited to case report series (Jenkins et al., 2000). Given the morphological overlap between reactive lymphoid hyperplasia and MZL, immunophenotypical testings are often required for definitive diagnosis. OAMZLs are positive for CD20, Bcl-2, PAX5, and CD79 A but typically do not express CD5, CD10, or CD23 (Lagoo et al., 2008). In the setting of CD5+, assessments of cyclin-D1 expression and FISH analysis for translocation t(11;14)(q13;q32) are helpful in differentiating these cases from mantle-cell lymphoma (Stefanovic and Lossos, 2009).

3.2.3.3. Treatment. Given its rarity, guidelines for treatment of PLL do not universally exist. The treatment decision requires a multidisciplinary approach, taking into account the extent of the disease, the impact of the lymphoma on the eye and visual function, and other prognostic factors. Various treatment modalities are available. Surgery as the only treatment modality should not be used, because the recurrent risk is relatively high in the absence of adjuvant treatment (Eckardt et al., 2013).

Some authors evaluated a "watch-and-wait" strategy in asymptomatic, stage IE PORL as an acceptable approach to postpone the initiation of treatment, in some cases even for several years (Tanimoto et al., 2006). Due to high variability across geographic regions for *Cp* infection in PORL and PLL patients, empiric antibiotherapy should be generally recommended (Husain et al., 2007).

External beam RT is considered the gold standard for stage IE PORL as it has been reported being very effective (Martinet et al., 2003; Parikh et al., 2015).Several series indicate that doses of at least 25 Gy were required to provide optimal LC (Ejima et al., 2006). However, significant ophthalmologic toxicities with vision loss was observed with doses greater than 36 Gy (Parikh et al., 2015). With the recommended dose of 30 Gy, most patients achieved CR, and the 5-year survival approached 90–100% with minimal local side effects (Parikh et al., 2015). In the *RCN* multicenter study with a median RT dose of 34.2 Gy, LC rate was 97%, and the 5-year DFS, OS, and CSS rates were 65%, 78%, and 87%, respectively (Martinet et al., 2003). In the case of LRR, low-dose RT at 2 x 2 Gy was effective and well tolerated, with durable LC (Fasola et al., 2013).

Reporting the use of CXT from few reports of small retrospective series makes it difficult to draw conclusions. CR was achieved in 67–100% of patients, but LR occurred in up to 29% of those. This emphasized the need and potential role of RT in the management of PORL (Stefanovic and Lossos, 2009). Rituximab was found to be

effective as front-line treatment, but required further investigations with longer follow-up (Annibali et al., 2015).

Radio-immunotherapy may be a useful approach in the treatment of PORL, and is currently being assessed in several ongoing phase 2 and 3 studies using ^{90}Y ibritumomab tiuxetan in low-grade NHLs (Lossos et al., 2015).

Various prognostic factors have been described. Most of authors agreed with the impact of IPI scoring and its components (age, PS, stage, EN site, and LDH level) for both OS and DFS (Jenkins et al., 2000; Martinet et al., 2003). Additionally, response to treatment and accurate staging were associated with better DFS (Martinet et al., 2003).

3.2.3.4. Conclusion and best practice. Accurate staging is fundamental for optimal treatment and outcome. PET-CT is more sensitive in detection of distant metastatic disease. Standard of care includes RT (30 Gy) for stage IE which is associated with excellent LC. CXT/immunotherapy should be considered for disseminated disease. Doxycycline 100 mg twice daily orally for 3 weeks can be given for patients with *Cp*-positive OAMZL.

3.3. Dual - function glands

Dual-function glands refer to organs that are capable of both endocrine and exocrine functions. For example, liver synthetizes many essential substances for release into blood stream, plays key roles in metabolism, and produces bile into gastrointestinal tract. Pancreas produces several important hormones participating in sugar control and metabolism; it also secrets pancreatic juice, assisting the digestive and absorptive processes of nutrients in the small intestine.

3.3.1. Primary hepatic lymphoma

There is no consensus on the exact definition of primary hepatic lymphoma (PHL). Lei et al. proposed criteria for identifying a PHL as: (1) symptoms caused mainly by liver involvement at presentation, (2) absence of distant lymphadenopathy, and (3) absence of leukemic blood involvement in the peripheral blood smear (Lei, 1998).

3.3.1.1. Epidemiology. PHL is rare and represents 0.4% of EN-NHLs (Loddenkemper and Longerich, 2008) (Loddenkemper C, 2008 #125). Most of the patients are middle-aged men (Page et al., 2001). The pathogenesis is not clear, but several etiologic factors have been proposed such as hepatitis infections and exposure to certain chemicals (Bronowicki et al., 2003).

3.3.1.2. Diagnosis. Clinical presentation is nonspecific. B-symptoms are frequently present. Hepatomegaly is common in at least 50% of the patients; abdominal pain and jaundice can also be found (Avlonitis and Linos, 1999; Noronha et al., 2005). PHL often presents as a solitary lesion (55–60% of patients); multiple lesions or hepatic diffuse infiltration are less common (Noronha et al., 2005). Radiological findings for PHL are usually non-specific. PHL appears as a hypo- or iso-attenuating lesion on US, hypodense nodule on tri-phasic liver CT-scan, and T1 hypointense, T2 slight hyperintense on liver MRI (Maher et al., 2001). Tumor markers for liver tumors such as AFP, CEA, CA 19-9 are usually normal. Liver biopsy is the most reliable tool for PHL diagnosis (Noronha et al., 2005; El-Sharkawi et al., 2011).

Most of PHL (46–68%) are DLBCL, and other histopathology types have been described in less than 5% of cases, including diffuse mixed large and small cell, lymphoblastic, diffuse immunoblastic, diffuse histiocytic, mantle cell, small non-cleaved, and Burkitt's lymphoma (Lei, 1998; Noronha et al., 2005).

3.3.1.3. Treatment. The optimal therapy remains unclear. Prognosis was believed to be dismal, since most of PHL patients present with unfavorable factors (advanced age, B-symptoms, hepatic dysfunction, and/or co-morbidities) (Lei et al., 1995). Distant failure can occur shortly after primary treatment. The median survival varies considerably (ranges, 3–124 months), rendering it impossible to estimate a general outcome (Noronha et al., 2005).

Surgical treatment are indicated for localized disease which can be resected completely, or with debulking surgery before or after CXT (Avlonitis and Linos, 1999). CXT can be given as upfront treatment for PHL. Because of the difficulties present in PHL diagnosis, many patients are diagnosed after liver resection; CXT can be given as an adjuvant treatment in this context. Early and aggressive anthracycline-based CXT may result in prolonged remissions (Noronha et al., 2005). The addition of rituximab increases the response rate, and prolongs survival in elderly patients without a clinically significant increase in toxicity (Coiffier et al., 2002; Sehn et al., 2005). Despite the radiosensitive feature of EN-NHLs, concerns about radio-induced liver disease from older data with conventional RT techniques have made RT more underutilized in PHL. Some authors suggest that the potential benefits of RT in the management of PHL, alone or concurrently with CXT, can result in long-lasting CR many years after (Avlonitis and Linos, 1999; Shin et al., 2006). RT certainly merits further investigations to prove its place in the treatment for liver tumors, including PHL. The largest and longest follow-up series of 41 PH L patients has been reported by *RCN* recently (Ugurluer et al., 2016), which described better outcomes than that was previously seen in the literature. The 5- and 10-year OS rates were 77% and 59%, respectively. Almost all of the patients had high-grade DLBCL, and received anthracycline-based CXT. RT doses at 30.6–40 Gy were given in 4 patients exclusively or in combination with CXT. The presence of fever, absence of weight loss, and normal hemoglobin level were independent favorable factors on outcomes. Others suggested a prognostic factor based on histopathologic subtypes: nodular PHL had better outcomes compared to diffuse PHL.

3.3.1.4. Conclusion and best practice. The rarity of PHL leads to diagnostic and therapeutic management problems. It is very important to obtain liver biopsies if there is a possible clinical suspicion for PHL. If confirmed pathologically, this disease is curable, and outcomes have improved with new therapeutic modalities. The optimal therapeutic approach remains unclear but CMT is encouraged in eligible patients even for nodular PHL, given the high rates of extra-hepatic recurrence that may occur in the future.

3.3.2. Primary pancreatic lymphoma

The diagnosis of primary pancreatic lymphoma (PPL) should meet all of the following criteria (Salvatore et al., 2000): (1) lymphomatous spread limited to only the pancreas and peripancreatic lymph nodes, (2) lack of splenic and hepatic involvement, and with no involvement of superficial or mediastinal lymph nodes, and (3) a normal leukocyte count in the peripheral blood.

3.3.2.1. Epidemiology. By respecting the definition of Dawson et al., PPL accounts for less than 0.5% of all pancreatic malignancies and 1% of EN-NHLs (Rock et al., 2012). Pancreatic involvement by NHL is more commonly the result of local extension or secondary involvement by widespread disease, rather than primary malignant transformation of a pancreatic lesion. Data from a retrospective series of 42 cases of hematologic malignancies involving the pancreas (during a period of 45 years) and an additional of 20 cases form autopsies (a 20-year period) showed that only 6 out of 62 patients could be diagnosed as PPL according to the strict criteria (Rock et al., 2012). Fewer than 150 cases of PPL have been identified in the literature as a result. It has been suggested that more than half of pancreatic NHL cases reported in the literature do not truly represent PPL, but rather pancreatic involvement of peripancreatic lymph nodes or more disseminated disease (Saif, 2006).

PPL occurs predominantly in male (M:F ratio of 13:3) and affects relatively older patients in their sixth decade of life. It presents more commonly in immunosuppressed individuals and may have a possible

Table 1
Diagnostic tools in extranodal lymphoma of the glands.

Localization	Radiographic exams	Histological sampling	Most common histology	CNS examination
Thyroid	Cervical US, CT-scan	FNA, biopsy	DLBCL	NS
Testis	Testis US, pelvic MRI	Orchiectomy	DLBCL	Yes
CNS	Brain MRI	Biopsy	DLBCL	Yes
Adrenal gland	Abdominal CT-scan	Biopsy[a]	DLBCL	Yes
Ovary	Pelvic CT-scan, MRI	FNA, biopsy	DLBCL	Yes
Salivary gland	Cervical US, MRI	FNA, biopsy	MALT	NS
Breast	Mammography, breast MRI	Biopsy	DLBCL	NS but strong consideration
Lacrimal gland	Cervico-facial CT-scan, MRI	FNA, biopsy	MALT	NS
Liver	Abdominal MRI	Biopsy	DLBCL	NS
Pancreas	Abdominal CT-scan, MRI	Biopsy	DLBCL	NS

a: after assessing catecholamine status, CT: computed tomography, CNS: central nervous system, DLBCL: diffuse large B-cell lymphoma, MALT: mucosa-associated lymphoid tissue, MRI: magnetic resonant imaging, NS: not systematic, US: ultrasonography.

Table 2
Treatment modalities in extranodal lymphoma of the glands.

Localizations	Radiotherapy			Surgery	Systemic treatment	Other modality
	Role	Dose, fractionnation	Target volume			
Thyroid	In CMT Exclusive (if MALT)	≥ 40 Gy, 2 Gy/fr	Entire thyroid	No	CHOP-based CXT	No
Testis	In CMT, after CXT	25-30 Gy, 1.5-2 Gy/fr 30-35 Gy (CR) or 35-45 Gy (CRu), 2 Gy/fr	Contralateral scrotum IFRT[b] in stage IIE	Inguinal orchiectomy	R-CHOP ≥ 6 cycles	CNS prophylaxis (ITC MTX)
CNS	WBRT[a]	24Gy (CR), 36-45 Gy (CRu), 40-50 Gy (exclusive), 1.5-1.8 Gy/fr 30-36 Gy (palliative), 2-3 Gy/fr	Whole brain	No	High-dose MTX-based CXT	No
Adrenal gland	No	NA	NA	No	R-CHOP	CNS prophylaxis
Ovary	Controversial	30-36 Gy, 1.8-2 Gy/fr	Ovary +/- IFRT according to risk of relapse	No	R-CHOP	CNS prophylaxis (ITC MTX or cytarabine)
Salivary gland	Exclusive In CMT (if DLBCL)	25-30 Gy, 1.8-2 Gy/fr	Whole unilateral salivary gland	No	R-CHOP (if DLBCL)	No
Breast	Central role in CMT	38-40 Gy, 2 Gy/fr	Whole breast	Lumpectomy	Anthracycline-based CXT R-CHOP (if DLCBL)	Consider CNS prophylaxis
Lacrimal gland	Gold standard	25-30 Gy, 1.5-2 Gy/fr	Entire orbit	No	No	Watch and wait Doxycycline if *Cp* +
Liver	Underused	30-40 Gy, 1.8-2 Gy/fr	Not precise	Primary, debulking or after CXT	Anthracycline-based CXT	No
Pancreas	In CMT	40-46 Gy, 1.8-2Gr/fr	Local RT	Only for histologic sampling	CHOP x 6 cycles	No

a: use of WBRT need to be carefully considered due to its toxicity, b: irradiated volume includes para-aortic and pelvic lymph nodes, CHOP: cyclophosphamide-doxorubicin-vincristine-prednisone, CMT: combined modality therapy, CNS: central nervous system, CR: complete response, CRu: unconfirmed complete response, CXT: chemotherapy, DLBCL: diffuse large B-cell lymphoma, fr: fraction, Gy: gray, IFRT: involved-field radiotherapy, ITC: intrathecal, MTX: methotrexate, NA: not applicate, R: rituximab, WBRT: whole brain radiotherapy.

causative link with EBV infection (Basu et al., 2007).

3.3.2.2. Diagnosis. Some authors suggested that the clinical presentations of isolated abdominal pain, B symptoms, and palpable mass without jaundice or diabetes mellitus and with normal level of CA19-9 is more suggestive of NHL, particularly in those who have a history of hematologic malignancies. More often, however, PPL can easily mimics an adenocarcinoma of pancreas. This makes tumor sampling for histologic evaluation mandatory, and must be done before all therapeutic decisions are finalized (Johnson et al., 2014).

High grade B-cell NHL is the most common histologic type (45% of cases), followed by low grade B-cell NHL and other subtypes of B-cell lymphomas; T-cell lymphomas, although rare, carry a dismal prognosis (Grimison et al., 2006).

3.3.2.3. Treatment and prognostic factors. As the diagnosis of a pancreatic mass cannot always be successfully made before surgery, many patients are diagnosed after primary surgical excision, partial pancreatectomy, or even Whipple's procedure. Aggressive surgical interventions, however, have no apparent impact on improving survival and are usually associated with increased complications, rendering it not generally recommended for diagnosis and treatment of PPL (Tuchek et al., 1993; Behrns et al., 1994). Surgery may have a role for alleviating gastrointestinal or biliary obstruction; however, generally non-surgical procedures such as endoscopic or percutaneous stent insertion should be encouraged.

When patients present after primary surgical resection, adjuvant CXT based on CVP or CHOP regimens are most often administered for 6 cycles. When the diagnosis can be obtained preoperatively, the treatment of choice for most PPL patients is CMT including anthracycline-based CXT and RT (Grimison et al., 2006). The addition of rituximab to CXT was well tolerated, and was shown to increase CR rate and prolong survivals in patients with DLBCL, without a clinically significant increase in toxicity even for elderly patients (Coiffier et al., 2002). PPL patients treated with rituximab had good outcome without evidence of disease at 2 years after treatment (Grimison et al., 2006).

The role of RT in the management of PPL is not well-established. Local RT up to a total dose of 40–46 Gy has been used as consolidation after CXT in PPL patients, offering cure rates up to 30% (Shahar et al., 2005; Grimison et al., 2006) which was considerably better than

patients with pancreatic adenocarcinoma.

IPI surrogates such as tumor burden and LDH levels represent the most important prognostic factors affecting outcomes of PPL. CMT is also a favorable factor for longer survival: up to 26 months in patients receiving CXT and IFRT, compared to 13 months in patients treated with CXT alone, and 22 months if only RT was administered (Salvatore et al., 2000). Histological subtypes were suggested to impact outcome in a Japanese study (Nishimura et al., 2001), with 1-year actuarial survival rate for B-cell lymphomas (52%) being better than that of T-cell lymphomas (0%).

3.3.2.4. Conclusion and best practice. Giving the similarity of clinical and radiological findings between PPL and pancreatic carcinomas, histopathological examination is mandatory for diagnosis and treatment planning of patients with suspicious PPL. Surgical resection and/or biopsy should be avoided unless percutaneous FNB is not accessible. Treatment of choice is CMT including anthracycline-based CXT and IFRT; rituximab can also be considered.

4. Conclusion

In this review, we have summarized relevant RCN-endorsed studies and the best contemporary practice in primary EN-NHL of glands. Tables 1 and 2 summarize the main diagnostic tools and treatment modalities in EN-NHL of the glands. We recognized that most of EN-NHL of glands are rare, whose existence was still a subject of debate. Evaluation and treatment approach are based on sites of involvement, histopathology types and prognostic factors. In the modern era, we've been greeting more and more success of novel immune-based therapies in the management of hematological malignancies such as next-generation anti-CD20 monoclonal antibodies, immune checkpoint inhibitors, engineering immune cells, radio-immunotherapy. These may also serve as potential trends for future research and management of EN-NHL, including EN-NHL of glands. A better understanding of molecular and genetic characteristics of these particular diseases is crucial for an appropriate management in the era of personalized treatment developments.

Conflict of interest

None.

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