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REVIEW

Primary Pancreatic Lymphoma: Recommendations for Diagnosis and Management

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Video abstract

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Background: Primary pancreatic lymphoma (PPL) is a rare disease representing 0.1% of all malignant lymphomas, which lacks well-defined diagnostic and therapeutic protocols. We conducted a systematic review to analyze demographic, diagnostic and therapeutic features of PPL.

Methods: This review identified small series and single case reports. Sources were MEDLINE, PubMed, and the Cochrane library from January 2001 to December 2020. Data were screened, extracted and the risk of bias analyzed by three independent reviewers.

Results: A total of 107 eligible papers (17 small series, 90 single case reports) describing 266 patients were identified. Patients had a median age of 53.1 (range 3–86) years and were males in 64.6% of cases. Abdominal pain and jaundice were the most common presenting symptoms, affecting 75.3% and 41.8% of patients, respectively. PPL had a median size of 60.6 mm (range 16–200) and it was localized in the pancreatic head in 63.7% of cases. At diagnosis most patients underwent ultrasonography followed by computed tomography. PPL typically showed low echogenicity, and lower contrast enhancement than solid tumors. Histopathological specimens were obtained by percutaneous or endoscopic biopsies in 47.7% of patients; abdominal surgery was performed in 33.5% of cases. Overall, diffuse large B-cell lymphoma was the most frequent histological diagnosis (53.6%). However, patients aged <18 years were affected by Burkitt lymphoma in 52.4% of cases. Most patients (53.6%) received immunochemotherapy (IC) or IC plus radiotherapy (14%). Demolitive surgery appeared to be associated with impaired survival. Central nervous system (CNS) relapse or progression was observed in 20% of patients.

Conclusion: PPL is a rare entity, with some peculiar features at modern imaging. For diagnostic purposes percutaneous or endoscopic biopsies might be preferable, as opposed to surgery. No definite data is available about the optimal treatment, which should be tailored on the histological type and associated with CNS prophylaxis.

Keywords: primary pancreatic lymphoma, diffuse large B cell lymphoma, Burkitt lymphoma

Introduction

Primary Pancreatic Lymphoma (PPL) is a rare disease representing only 0.1% of malignant lymphomas, 0.6% of extranodal lymphomas, and 0.2% of all pancreatic tumors.[1,2] On the contrary, secondary pancreatic involvement occurs quite commonly in lymphomas, especially in the presence of widespread nodal or extranodal disease, and may be observed in up to 30% of cases.[3]

Over the years, different definitions of PPL have been suggested.[3,4] More recently, the World Health Organization (WHO) has provided the following diagnostic criteria: i) the bulk of disease has to be located in the pancreas, ii) although

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adjacent lymph nodes involvement and distant spread may exist, the primary clinical presentation has to involve the pancreatic gland.[5]

PPL can develop at any age, but usually affects elderly patients, with a male prevalence. Immunosuppression, related to HIV infection or solid organ transplantation, may favor its development.[6] From a clinical standpoint, the main presenting symptom of PPL is the abdominal pain. However, other common clinical findings include systemic symptoms (fever, night sweats and weight loss), jaundice, pancreatitis and/or gastric or duodenal obstruction.[2,7,8] Overall, these symptoms resemble those of other pancreatic diseases, often resulting in diagnostic problems.[9,10] PPL can be located in any portion of the gland, but it mainly involves the pancreatic head, which contains the greatest amount of lymphoid tissue.[9] Histopathological analysis is usually consistent with diffuse large B cell lymphoma (DLBCL) not otherwise specified (NOS); nevertheless, other subtypes of lymphomas, including marginal zone lymphoma (MZL) or follicular lymphoma (FL), may be detected.[5,9,10] Anecdotal cases of Hodgkin (HL) and T cell non Hodgkin lymphoma (T-NHL) have been also described.[11,12]

A diagnosis of PPL can be obtained through percutaneous/endoscopic biopsy, exploratory laparotomy or demolition surgery.[7] With regard to treatment, no definite guidelines can be drawn from literature. In fact, most reports on PPL are retrospective and describe undersized and heterogeneously treated groups of patients.

The aim of this review was to retrieve, analyze and summarize data obtained from case collections and single case reports published in the last two decades.

The final goal was to identify specific characteristics of this rare lymphoma entity in order to provide evidence to establish future diagnostic and therapeutic guidelines.

Methods

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis guidelines.[13] We conducted an extensive systematic literature search since 01 January 2000 through 31 December 2020. Sources were PubMed, Medline, and Cochrane library. We deemed eligible all types of reports (case collections and single cases). This search was limited to studies published in English.

The eligibility criteria were (a) adult and pediatric population (b) pancreatic lymphomas fulfilling diagnostic criteria for PPL according to WHO.[5]

All titles were downloaded into an Endnote library and duplicated removed automatically. Three reviewers (DF, EB, CV) screened the titles and abstracts for eligibility. Then full text was screened again. A senior reviewer (CT) resolved any disagreement. For each article, at least one reviewer extracted the following information: demographics, presenting symptoms, diagnostic methods, and histological classification. Whenever available data about treatment and outcome were also retrieved.

A total of 107 papers reporting on 266 patients were deemed eligible.[10–12,14–113] Figure 1 provides the PRISMA flow diagram.

Percentages regarding each item analyzed were calculated based on the number of available data as specified in each table.

Results

Demographics and Clinical Characteristics

Among the 266 patients retrieved from literature, 172 (64.6%) were males, 94 (35.4%) females. The mean age was 53.1 (range 3–86) years. Twenty-one (7.9%) patients were aged less than 18 years.

As reported in Table 1, abdominal pain (75.4%) was the most common presenting symptom, followed by jaundice (41.8%), and B symptoms such as fever, night sweats and weight loss (31.9%). Acute pancreatitis and gastric or duodenal obstruction were the first clinical presentation in 25.9% and 10.7% of patients, respectively. Two patients were immunosuppressed after a simultaneous pancreas-kidney transplant.[61,107]

Laboratory Tests

Pretreatment laboratory tests were available for a minority of patients. Serum levels of lactate dehydrogenase (LDH) were elevated in 50.4% of patients, carbohydrate antigen 19–9 (CA 19–9) in 26.9%. The blood count showed anemia in 20.9% of patients, leukocytosis (>10.000/mmc) in 18.3%, and thrombocytopenia in 4.8%. Laboratory tests are reported in Table 1.

Imaging

Imaging features were available in 256 patients (Table 2). PPL had a mean size of 60.6 mm (range 16–200) and it was located in the pancreatic head in 163 (63.7%) cases. Early-stage Ann-Arbor disease (I–II) was diagnosed in 76% of patients, advanced (III–IV) in the remaining 24%.

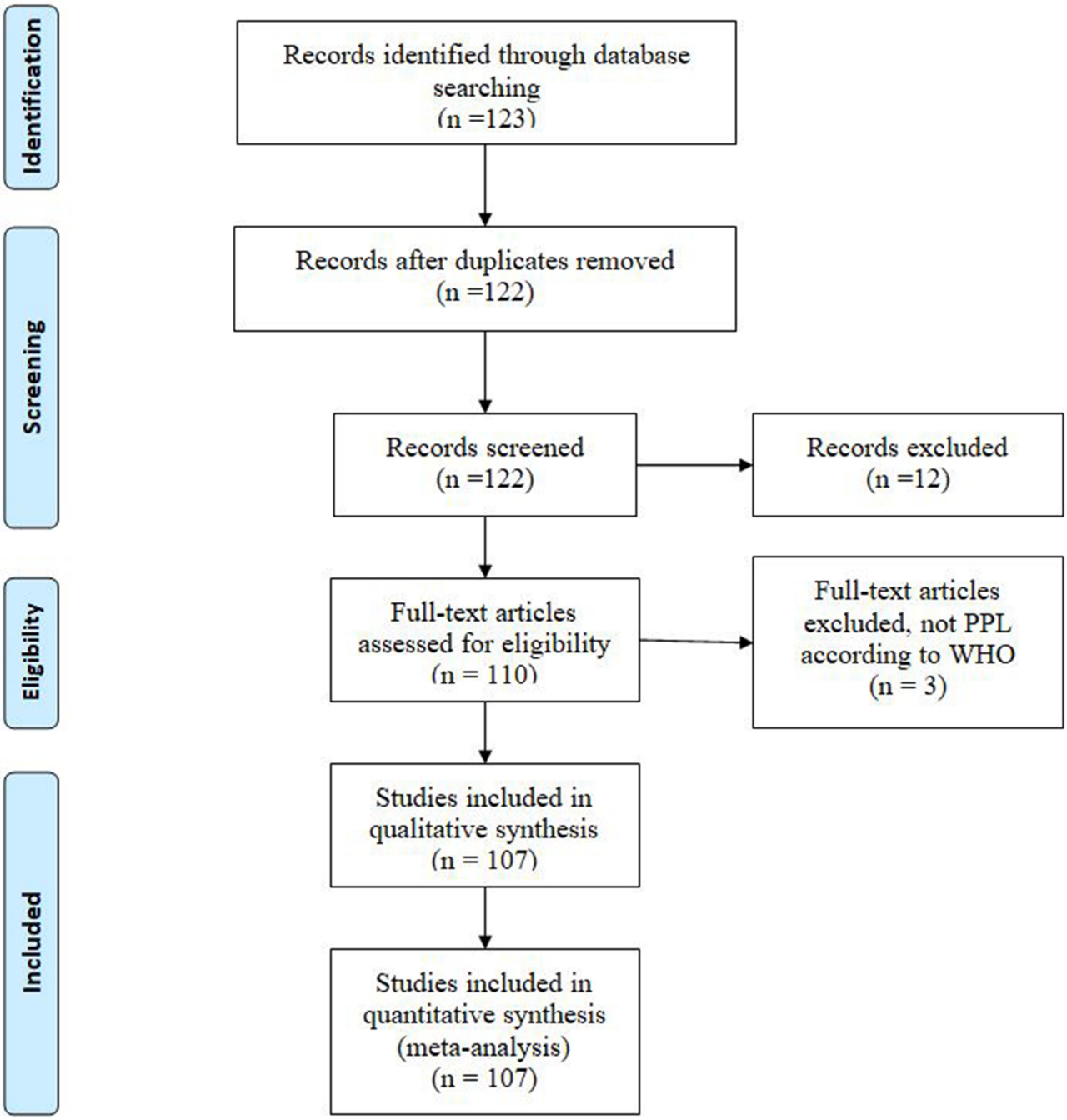

Figure 1 PRISMA flow diagram.

Ultrasonography (US) was performed in 214/256 patients (83.6%) at disease onset. Computed tomography (CT) was performed in 249/256 cases (97.3%), often following US; multidetector technology and contrast agent enhanced protocols were always used.

Magnetic Resonance Imaging (MRI) was performed in 36/256 cases (14.0%), nuclear medicine, in particular positron emission tomography-CT (PET-CT) with evaluation of 18fluoro-2-deoxy-d-glucose (^{18}FDG) intake, in 51/256 patients (19.9%).

US is extensively used since it enables a rapid evaluation of pancreas size, borders, echostructure and vessels.[54,92] The most common finding is enlargement of the parenchyma, focal or diffuse; the affected pancreas presents also lower echogenicity, appearing darker than normal. At color-Doppler evaluation major vessels can be surrounded by

Table 1 Patient Characteristics

Characteristics	n (%)
Presenting symptoms	
Abdominal pain	175/232 (75.4)
Jaundice	100/239 (41.8)
B symptoms	77/241 (31.9)
GI obstruction	24/225 (10.7)
Acute pancreatitis	56/218 (25.9)
Laboratory values	
LDH > upper limits	65/129 (50.4)
CA 19–9 > upper limits	32/119 (26.9)
Anemia	19/91 (20.9)
Thrombocytopenia	4/84 (4.8)
WBC > 10.000/mmc	17/93 (18.3)

Abbreviations: GI, gastrointestinal; LDH, lactate dehydrogenase; CA, carbohydrate antigen; WBC, white blood cells.

Table 2 Imaging Characteristics

Imaging	n (%)
Imaging method	
US	214/256 (83.6)
CT	249 (97.3)
MRI	36 (14.1)
PET-CT	51 (19.9)
Pancreatic localization	
Head	163/256 (63.6)
Body-tail	76 (29.6)
All gland	17 (6.6)
Tumor diameter, mean (range)	60.6 mm (range 16–200 mm)

Abbreviations: US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-CT.

pathological tissue, but always patent (contrary to other solid neoplasms like adenocarcinoma).[110,114] When a pancreatic disease is identified by US a second line radiological examination, usually CT, is mandatory.

At CT, PPL presents as a large solid lesion, potentially involving the whole gland; contrast enhancement is lower than healthy pancreas. Fat stranding in the peri-pancreatic region is typical; dilation of the bile and pancreatic duct is not common, contrary to pancreatic adenocarcinoma. Vascular encasement can be observed, without irregularities in vessels wall.[51,88,114]

MRI can be used if CT is inconclusive or to avoid radiation exposure in younger patients. Involved parenchyma shows lower signal intensity on T1-weighted images and higher signal on T2-weighetd images compared to healthy pancreas; diffusion-weighted sequences present very high sensitivity to depict lymphomatous tissue and lymph nodes.[114] PET-CT is indicated to assess the metabolic activity of the primary neoplasm and to depict involved lymph nodes in the whole body.[98]

Diagnostic Procedures and Histological Assessment

Information about diagnostic procedures was available in 224 patients (Table 3). Histopathological specimens were obtained mostly by percutaneous or endoscopic biopsies in 68 (30.3%) and 39 (17.4%) cases, respectively. Fine needle aspiration (FNA) was performed in 33 (14.8%) cases, abdominal surgery in 75 (33.5%) (26 surgical biopsy, 49 demolition surgery). Demolition surgery consisted mainly of Whipple procedure and spleno-pancreasectomy. In the remaining 9 (4.0%) patients the diagnosis was autoptic. The main histological diagnosis was DLBCL in 143 (53.6%) patients, followed by FL in 26 (9.8%) and BL in 20 (7.5%). In 31 (11.6%) cases the histology was not specified. Overall, this data is in agreement

Table 3 Diagnostic Methods, Histology and Clinical Stage

Diagnosis	n (%)
Diagnostic method	
Percutaneous biopsy	68/224 (30.3)
Endoscopic biopsy	39 (17.4)
FNA	33 (14.8)
Surgical biopsy	26 (11.6)
Demolition surgery	49 (21.9)
Autopsy	9 (4.0)
Histology	
DLBCL	143/266 (53.6)
FL	26 (9.8)
BL	20 (7.5)
High grade B cell lymphoma	14 (5.2)
T-NHL	18 (6.7)
HL	4 (1.5)
LPL	4 (1.5)
MZL	2 (0.7)
SLL	2 (0.7)
PTLD	2 (0.7)
Lymphoblastic lymphoma	1 (0.4)
Unknown	31 (11.6)
Clinical stage (Ann Arbor)	
I–II	152/200 (76)
III–IV	48/200 (26)

Abbreviations: FNA, fine needle aspiration; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; BL, Burkitt lymphoma; NHL, non Hodgkin lymphoma; HL, Hodgkin lymphoma; LPL, lymphoplasmacytic lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; PTLD, post-transplant lymphoproliferative disorder.

with that reported by a recent paper by Mukhija et al[115] evaluating 835 patients affected by pancreatic lymphomas, though the analysis was not restricted to the PPLs only.

According to data published in literature, percutaneous or endoscopic biopsies are reliable and scarcely invasive. On the other hand, despite providing a significant diagnostic accuracy for adenocarcinoma (sensitivity of 86.8% [95% CI 85.5–87.9] and specificity of 95.8% [95% CI 94-6-96.7]),[116] endoscopic ultrasound guided fine needle aspiration (EUS-FNA) is a poor diagnostic tool for lymphoma.[117] Immunophenotypic analysis may be useful to integrate cytology.[118,119] In a study involving 11 patients with PPL, cytology alone revealed a correct diagnosis in 28% compared to 100% by integrated immunophenotype.[118] However, tissue architecture in addition to cytomorphology is crucial in the diagnosis of lymphoma. Overall, a non-invasive diagnostic approach is preferable to demolition surgery, which was associated with a higher mortality rate.[10,34,51,120] Figure 2 shows the temporal variation in biopsy techniques.

Treatment and Pattern of Relapse

Information about treatment was available in 207 of the 266 patients retrieved from literature (Table 4). The initial treatment consisted of immunochemotherapy (IC) alone in 111 patients (53.6%), IC plus radiotherapy (RT) in 29 (14.0%), RT alone in 1 case (0.5%), and demolition surgery in 59 (28.5%). Surgery alone was reserved to 15 patients, it was followed by IC in 39, RT in 3 and both IC and RT in 2 cases. Seven patients (3.4%) were not treated at all.

There is no consensus on the ideal treatment approach for PPL patients; studies from the pre-rituximab era suggested an aggressive local management of disease with demolition surgery.[3,34] In contrast, more recent papers suggested a less invasive approach with IC as the cornerstone of treatment.[121,122] There is no consensus on the role of RT in patients affected by PPL.[39]

Among 169 patients for whom a follow up was provided, 30 (17.7%) presented a disease relapse after a median time of 15 months (range 2–108 months).[10,19,28,33,49,51,53,64,73,101] Interestingly, 6 relapses (20%) (2 DLBCL, 2 BL, 1 T-NHL, and 1 high grade B cell lymphoma) involved the CNS.

PPL in the Pediatric Population

Our analysis identified 21 cases of PPL in patients under 18 years of age.[15,24,30,35,37,51,55,67,70,81,82,84,87,92,96,99–102] The mean age was 10.3 (range 3–16) years, with most of patients (19, 90.5%) being males (Table 5).

As in adults, the main presenting symptom was abdominal pain. The percentage of jaundice was higher than in adults (61.9% vs 39.9%), while the number of patients aged <18 years with B symptoms was very low (9.5% vs 34.1%). Interestingly 10 patients (47.6%) had an acute pancreatitis at disease onset.

Laboratory tests, compared to adults, showed elevated LDH values in the large majority of patients (80% vs 47.9%), while CA 19–9 never increased (0% vs 27.6%).

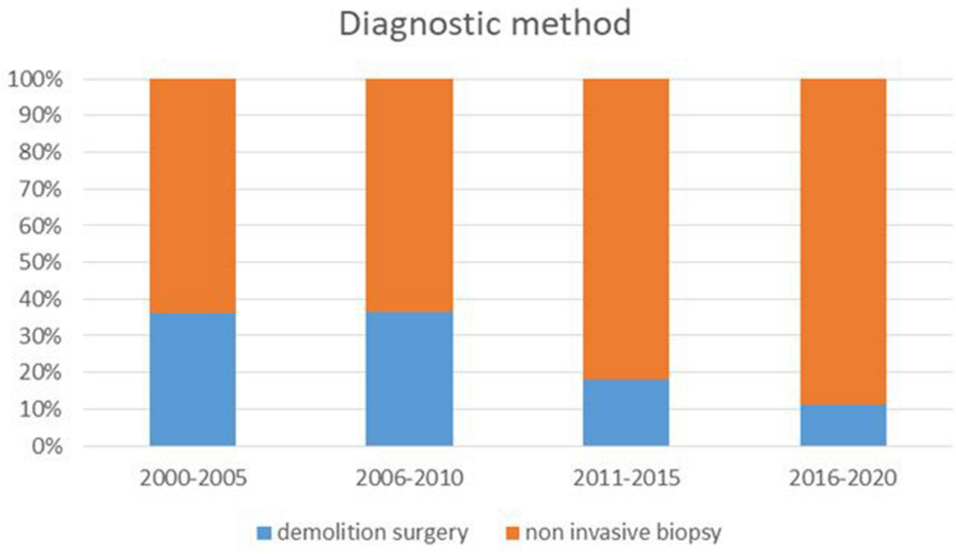

Figure 2 Temporal variation in biopsy techniques.

Table 4 Patient Survival According to Treatment and Histology

	Alive		Deceased	
	n (%)	OS, Months (Range)	n (%)	TTD, Months (Range)
Treatment*				
DS	4 (50)	11 (3–19)	4 (50)	2.5 (1–6)
DS-IC	13 (76.47)	37.8 (4–160)	4 (23.53)	13.5 (8–27)
DS-RT	2 (100)	34 (6–62)	/	/
DS-IC-RT	2 (100)	44.5 (24–65)	/	/
IC	26 (74.28)	34.7 (5–192)	9 (25.72)	13.4 (1–88)
IC-RT	15 (78.94)	45.4 (2–128)	4 (21.06)	36.5 (9–67)
Histology**				
DLBCL	48 (68.57)	39.3 (2–132)	22 (31.43)	18.9 (1–88)
FL	11 (84.61)	31.4 (6–62)	2 (15.39)	67 (63–72)
T-NHL	3 (23.07)	10.3 (4–15)	10 (76.93)	4.3 (0–8)
BL	8 (66.66)	63.25 (8–192)	4 (33.34)	2.9 (1–7)
HGBCL	3 (50)	34 (3–94)	3 (50)	10.3 (8–12)

Notes: *Data available in 83 patients; **data available in 113 patients.
Abbreviations: OS, overall survival; TTD, time to death; DS, demolition surgery; IC, Immuno-chemotherapy; RT, radiotherapy; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; NHL, non Hodgkin lymphoma; BL, Burkitt lymphoma; HGBCL, high grade B cell lymphoma.

Table 5 PPL Characteristics in Pediatric vs Adult Patients

Characteristics	Patients <18 Year n (%)	Patients >18 Years n (%)
Presenting symptoms		
Abdominal pain	16/21 (76.2)	159/211 (75.4)
Jaundice	13 (61.9)	87/218 (39.9)
B symptoms	2 (9.52)	75/220 (34.1)
GI obstruction	1 (4.76)	23/204 (11.3)
Acute pancreatitis	10 (47.6)	55/197 (27.9)
Laboratory values		
LDH > upper limits	8/10 (80)	57/119 (47.9)
CA 19–9 > upper limits	0/3 (0)	32/116 (27.6)
Pancreatic localization		
Head	13/21 (61.9)	150/235 (63.8)
Body-tail	2 (9.5)	74 (31.5)
All gland	6 (28.6)	11 (4.7)
Histology		
DLBCL	5/21 (23.8)	138/245 (56.3)
BL	11 (52.4)	9 (3.7)
High grade B cell lymphoma	1 (4.8)	13 (5.3)
T-NHL	2 (9.5)	17 (6.9)
Unknown	2 (9.5)	29 (11.8)
Clinical stage (Ann Arbor)		
I–II	5/13 (38.5)	147/187 (78.6)
III–IV	8 (61.5)	40/187 (21.4)

Abbreviations: GI, gastrointestinal; LDH, lactate dehydrogenase; CA 19–9, carbohydrate antigen; WBC, white blood cells; DLBCL, diffuse large B cell lymphoma; BL, Burkitt lymphoma; NHL, non Hodgkin lymphoma.

The mean size was similar (56.6 mm vs 61.1 mm) and also the pancreatic location, with a predilection for the pancreatic head (61.9% vs 63.8%).

Interestingly, in the pediatric cohort the main histological diagnosis was BL in 11 (52.4%), DLBCL in 5 (23.8%) patients.

Ng et al[123] reviewed the imaging findings of 80 children affected by NHL, with pancreatic involvement being present in 3 cases (3.75%). Similarly, Vade and Blane[124] reviewed the diagnostic imaging of 19 pediatric patients with BL and found 2 children with pancreatic involvement (10%).

The initial treatment consisted of IC alone in 16 patients (88.9%), and chemotherapy after demolition surgery in 2 (11.2%). Information about follow-up was available in 15 patients only. Fourteen/15 (93.3) reached a complete remission (CR) with first line therapy and one patient had a CNS relapse during the observation period.[101] These 2 patients were rescued with high dose chemotherapy plus autologous stem cell transplantation. With a median follow-up of 56.43 (range 8–132) months all patients were alive and in CR.

Discussion

This study presents data (diagnosis, histology, treatment and outcome) retrieved from 107 papers published from 2000 to 2020 on PPL.

As compared to pancreatic adenocarcinoma, which usually manifests in the 60- to 80-year-old age group,[125] PPL is usually diagnosed in younger adults (mean age 53 years). As previously described, the presentation of PPL may overlap with the onset of other neoplastic or inflammatory pancreatic diseases.[126,127]

Interestingly, in spite of symptoms and radiological findings (pancreatic head involvement) overlapping those of pancreatic ductal adenocarcinoma and autoimmune pancreatitis, some findings may indicate a diagnosis of PPL. For instance, a relatively large tumor size (>60 mm) together with the presence of distant lymph nodes at radiological assessment may suggest a diagnosis of lymphoma.[114] Unfortunately, few reports reported laboratory data, so it is not clear whether a elevate LDH value associated with CA 19–9 within the normal range may suggest a diagnosis of PPL, as previously indicated by our group.[51] Concerning the diagnostic approach, in more than half of cases reported in literature, tumor samples were collected through a noninvasive procedure: transcutaneous biopsy in 30.3%, endoscopic in 17.4% and FNA in 14.8%. However, in a significant number of patients, a surgical biopsy (11.6%) or a demolition surgery (21.9%) were performed. Worth of note, demolitive surgery was more frequently performed in the earlier time frame of our analysis, while noninvasive methods were preferred in most recent years (Figure 2). Finally, in 4.0% the diagnosis was obtained post-mortem.

In regard to histology, PPL was mostly classified as DLBCL (53.6%), FL (9.8%) and BL (7.5%). However, other types of lymphoma were described, including a non-negligible number of T-NHL (6.7%) and 5.2% of high-grade B cell lymphomas. Therefore, an accurate histological diagnosis should be obtained in order to provide patients with the best available treatment. It is interesting to note that among the 21 (7.9%) patients aged <18 years, BL was the prevalent histological type (52.4%). Unfortunately, a detailed histological classification according to the new 2016 WHO classification of lymphomas[128] was difficult to establish based on data reported by most of the articles here revised.

The lack of large PPL study series hampers definitive conclusion about the optimal treatment, which should rely on the histological subtype. According to our revision, chemotherapy with or without rituximab was the standard of care in most patients (53.6%), sometimes associated to RT (14.0%) or following diagnostic debulking surgery (18.9%). Overall, 26.1% of patients underwent a probably unnecessary surgical treatment.

Similarly to what has been described in the literature for other extranodal lymphomas,[129] the recurrence rate was high, at least according to the larger case series (23.52% and 34.21%, respectively).[10,51] Extranodal lymphomas may have different patterns of relapse depending on the tissue/organ involved. The CNS-International Prognostic Index (IPI) considers some primitive lymphoma sites (kidney and adrenal gland) as at increased risk of CNS relapse without taking into account pancreas.[130] Importantly, according to this literature search, in agreement with our previous findings,[51] patients affected by PPL had a relatively high incidence of CNS relapses (20% of the relapses reported). Obviously, no definitive conclusions can be drawn given the relatively small number of patients considered, and their heterogeneity in regard to histology and therapy received.

In conclusion, PPL represents a rare and challenging disease with relatively non-specific symptoms. Most PPLs are DLBCL in adults, BL in children. According to literature, a noninvasive approach should be the preferred diagnostic method. The diagnosis of PPL should be suspected also in pediatric cases. Because reported studies have been retrospective, used undersized patient groups and involved heterogenous regimens, no conclusions can be drawn for an optimal regimen, that should be tailored on histological subtype. The high CNS relapse rate reported in available literature, suggests that patients with PPL may benefit from a CNS directed prophylaxis.

Disclosure

The authors report no conflicts of interest in this work.

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