

Review

Clinical Target Volume in Biliary Carcinoma: A Systematic Review of Pathological Studies

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Abstract. *Background/Aim:* Radiotherapy is a treatment option for both adjuvant and neo-adjuvant settings for biliary tract cancer. Guidelines on the delineation of the target volume of lymph nodes are lacking; only generic indications are available, without specific recommendations for different primary tumour locations (e.g. intrahepatic, extrahepatic biliary tract or gallbladder cancer). The aim of this study was to systematically review available literature to provide recommendations on lymph node target volume delineation in patients with unresectable biliary tumour. *Materials and Methods:* A systematic search of electronic databases was performed up to July 2016. The primary outcome measure was the rate of lymph node involvement according to the location of primary biliary tumour. Sites with $\geq 5\%$ of nodal metastases were considered in the clinical target volume for radiotherapy planning. *Results:* Twelve

studies (1075 patients) were included. The most frequent site of lymph node metastasis in intrahepatic biliary tree carcinoma was retroportal (61.1%, 95% confidence interval (CI)=50.7-70.6%). Other frequently involved lymph nodes were along the hepatoduodenal ligament [frequency=38.7%, 95% CI=31.0-47.0%], those along the common hepatic artery (17.0%, 95% CI=8.2-31.9%) and the hilar nodes (16.9%, 95% CI=13.2-21.4%). In extrahepatic biliary tree cancer, the most frequently involved lymph nodes were the pericholedochal (42.7%, 95% CI=33.8-52.1%) and those along the hepatoduodenal ligament (40.3%, 95% CI=32.4-48.8%). Other commonly involved nodal regions included retroportal lymph nodes (30.9%, 95% CI=23.0-40.1%), pancreaticoduodenal anterior and posterior nodes (30.1%, 95% CI=12.2-57.1%), those along the common hepatic artery (19.7%, 95% CI=11.8-31.0%) and para_aortic nodes (15.2%, 95% CI=8.0-27.0%). The most common site of metastases in gallbladder cancer were the pericholedochal nodes (25.2%, 95% CI=18.6-33.2%), those along the cystic duct (23%, 95% CI=16.6-30.8%), and retroportal nodes (17.1%, 95% CI=11.6-24.5%). *Conclusion:* Biliary tract cancer has a high propensity for regional lymphatic metastases. An evidence-based nodal target definition of biliary tract cancer based on primary tumour location was proposed.

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Biliary tract cancer (BTC) is quite rare, representing 3% of all gastrointestinal tumours (1). BTCs are divided into intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma and,

finally, gallbladder tumours. These tumours arise from the epithelium lining biliary ducts and the most frequent histological type is adenocarcinoma (90%) (2). Prognosis is dismal and the only potentially curative option is surgery. Unfortunately, most patients have locally advanced disease at diagnosis and are not suitable for resection. Concurrent chemoradiation is used in both adjuvant and palliative settings (3). In patients with complete resection, the 5-year overall survival rates are 5-10% for those with gallbladder cancer and those with 10-40% for cholangiocarcinoma (1). After surgery, patients have a high risk of recurrence, thus justifying the use of adjuvant local treatment. A systematic review showed that adjuvant radiotherapy improves overall survival in those with extrahepatic primary tumour location (4). In particular, patients with positive lymph nodes with/without positive surgical margins experience the greatest benefit (5). Furthermore, chemoradiation represents an important option for locally advanced disease, since it improves the pain control and survival (6).

Modern radiotherapy techniques (three-dimensional conformal radiotherapy-(3D-CRT) and intensity-modulated radiation therapy (IMRT) allow optimal qualitative treatment with reduced toxicity. When planning treatment using these modern radiotherapy techniques, the target volume must be accurately and precisely defined. Despite this, guidelines on the delineation of the target volume of lymph nodes are surprisingly lacking. Only non-specific generic indications not stratified according to the primary tumour location are available (7).

The aim of the current study was to systematically review the available evidence in order to provide practical recommendations for the lymph node target volume delineation in patients with unresectable biliary cancer.

Materials and Methods

Data sources and search strategy. We performed a comprehensive literature search by using PubMed, SCOPUS, Google Scholar and the Cochrane Library (up to 31st of July 2016) to identify full articles evaluating lymph node involvement in biliary tract cancer. Electronic searches were supplemented by manual searches of references of included studies and review articles.

We identified studies using the following medical subject headings (MeSH) and key words: "biliary tract neoplasms" and "lymph nodes". The search was restricted to English language and full text.

The Medline search strategy was: ("biliary tract neoplasms"[MeSH Terms])OR ("biliary"[All Fields] AND "tract"[All Fields] AND "neoplasms"[All Fields]) OR "biliary tract neoplasms"[All Fields] OR ("biliary"[All Fields] AND "cancer"[All Fields]) OR "biliary cancer"[All Fields] AND ("lymph nodes"[MeSH Terms] OR "lymph nodes"[All Fields] AND "nodes"[All Fields]) OR "lymph nodes"[All Fields] OR ("lymph"[All Fields] AND "node"[All Fields]) OR "lymph node"[All Fields] AND involvement[All Fields].

Eligibility criteria. We included retrospective and prospective human studies. Only studies published in English were included in this review. All studies reporting data on resected biliary tree (intrahepatic, extrahepatic) and gallbladder cancer including lymphadenectomy, independently of the surgical technique in terms of tumour resection and lymph node dissection, were considered eligible. Exclusion criteria were the enrolment in the study of patients who had undergone resection without lymph node dissection and lack of data about the rate of nodal metastases at the different lymph node stations.

Data extraction. For each study, The following data regarding the incidence of lymph node involvement in patients with biliary tree cancer who underwent surgical resection were extracted according to tumour location: number of examined lymph nodes, dissected lymph node stations, and number and site of metastatic lymph nodes. Information about study design, period of enrolment, study location, number of patients, and population characteristics (gender and mean age) were also collected.

Outcome assessment. Primary outcome measures were the rate of lymph node involvement according to the tumour location (as intrahepatic, extrahepatic biliary tract and gallbladder). Based on the lymph node involvement reported in each study, the pooled rates of the involvement of each lymph node station were calculated according to the primary tumour location. Finally, we proposed to include only stations with an incidence of nodal metastases $\geq 5\%$ in the clinical target volume (CTV) for radiotherapy planning.

Study selection and quality assessment. Three independent researchers (IM, AG, VP) screened citations at the abstract level to identify potentially relevant studies and case series. Potentially eligible citations were retrieved for full-text review, with disagreements resolved by a fourth researcher (AGM). We obtained the following information from each report: author identification, year of publication, number of patients with positive lymph nodes on surgery, number of total examined patients in each article, number of node-positive patients for every lymph node station based on primary tumour location.

Statistical methods. The pooled rate was calculated by dividing the sum of patients with lymph node involvement in a specific lymph node station by the total number of patients with lymph node evaluation of the same station. Proportions were pooled by means of a random-effects model (8), and then presented as point estimates and 95% confidence intervals (CI). The main analysis was performed using Comprehensive Meta-Analysis 3.3.070 (Biostat, Englewood, NJ, USA).

Results

Search results. Through the step of screening the title and the abstract, 35 articles were identified. After full text review, 23 articles were excluded, since they did not report the rate of lymph node stations separately. Therefore, 12 studies were finally included (9-20) The flowchart of the selection process is shown in Figure 1. Of the 12 studies, six were on intrahepatic bile duct tumours (584 patients), four on extrahepatic bile duct cancer (244 patients), and three on gallbladder cancer (247 patients) (one study was on both intra- and extrahepatic tumours. Table I shows the characteristics of the included studies.

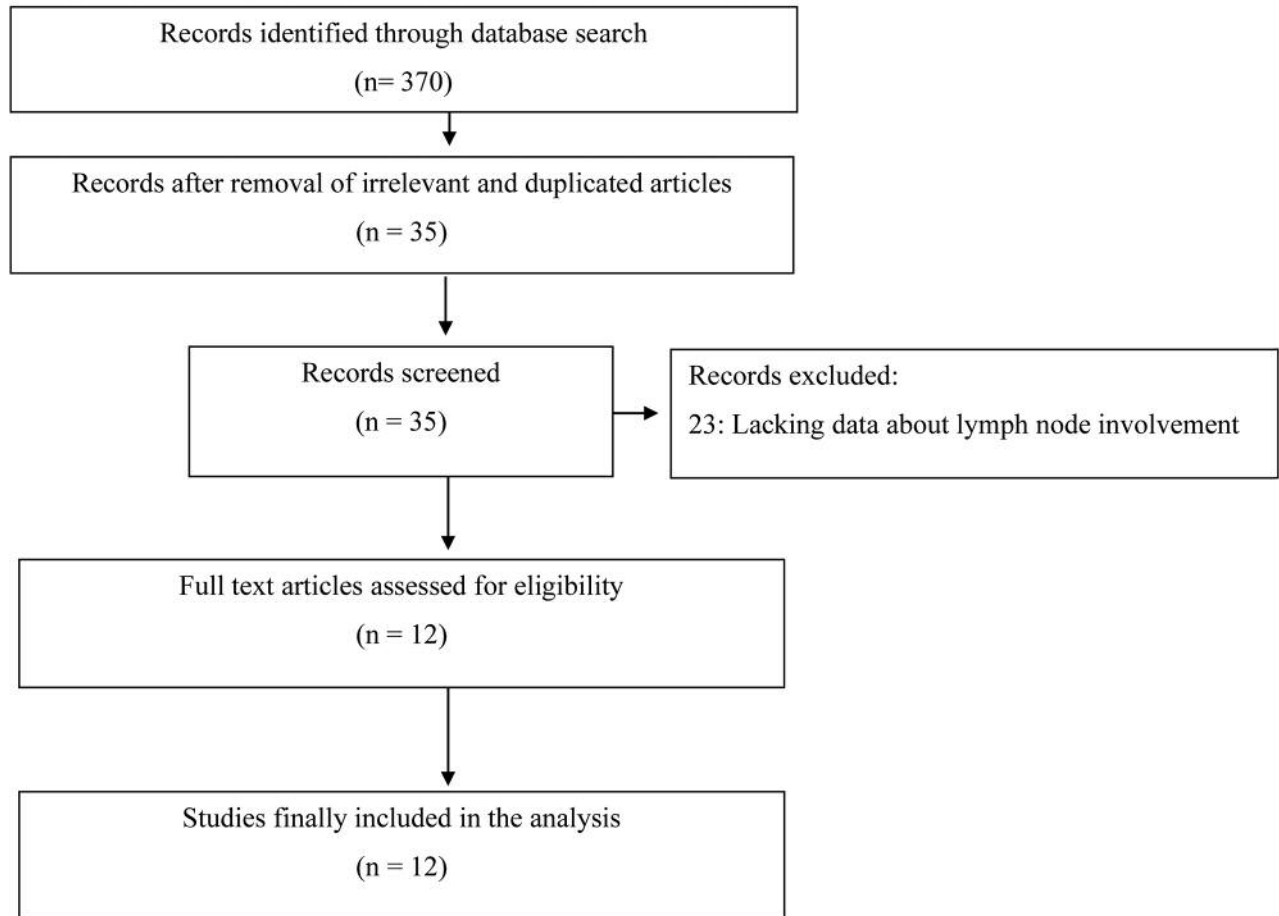


Figure 1. Flow chart of systematic search and review process.

Table I. Study characteristics.

Cancer site	Author, year (Ref no.)	Inclusion period	Study design	Study location	Sample size	Median age, years	Male gender, n (%)	Median no. of LNs dissected per patient (range)	Patients with lymph node metastases
Intrahepatic	Tsuji <i>et al.</i> , 2001 (9)	1980-1998	Retrospective	Japan	39	58.7 (41-76)	27 (69%)	32 (10-49)	62.0%
	Nagakawa <i>et al.</i> , 2005 (10)	1983-2004	Retrospective	Japan	30	NS	NS	NS	43.0%
	Yamamoto <i>et al.</i> , 1999 (11)	1980-1996	Retrospective	Japan	51	NS	NS	NS	45.0%
	Guglielmi <i>et al.</i> , 2013 (12)	1990-2012	Retrospective	Italy	54	NS	NS	55 (1-33)	33.3%
	Jiang <i>et al.</i> , 2010 (13)	1999-2008	Retrospective	China	90	NS	52 (58%)	NS	93.3%
	Chen <i>et al.</i> , 2011 (14)	2000-2010	Retrospective	China	320	57 (18-99)	184 (58%)	NS	23.8%
Extrahepatic	Guglielmi, <i>et al.</i> , 2013 (12)	1990-2012	Retrospective	Italy	72	NS	NS	79 (1-27)	41.7%
	Yoshida <i>et al.</i> , 1999 (15)	1983-1998	Retrospective	Japan	42	64 (35-78)	28 (67%)	320 (21-48)	60.0%
	Yoshida <i>et al.</i> , 1998 (16)	1995-1996	Retrospective	Japan	20	NS	NS	NS	55.0%
	Kitagawa <i>et al.</i> , 2001 (17)	1983-1998	Retrospective	Japan	110	60 1 (24-78)	80 (73%)	24 1	52.7%
Gallbladder	Negi <i>et al.</i> , 2011 (18)	2003-2009	Retrospective	India	57	46 (42-58)	13 (23%)	NS	58.0%
	Kondo <i>et al.</i> , 2002 (19)	1982-1999	Retrospective	Japan	112	64 (33-82)	41 (37%)	NS	58.9%
	Liu <i>et al.</i> , 2013 (20)	1995-2010	Retrospective	China	78	59 (33-82)	32 (41%)	4 (1-24)	47.4%

LN: Lymph node; NS: not specified.

Table II. Distribution of lymph node involvement (LNI) in intrahepatic biliary tract carcinoma.

Author, year (Ref no.)	No. patients with LNI/total patients	Location of LNI, number of patients (%)																
		HI	PD	HD	CHA	PA	RP	LG	SMA	CE	LC	CA	CD	PC	RPR	SA	PI	SI
Tsuji <i>et al.</i> , 2001 (9)	24/39	X	X	20 (51.3)	12 (30)	11 (28.2)	7 (18)	6 (15.3)	5 (12.8)	5 (12.8)	3 (7.6)	1 (2.5)	X	X	X	X	X	X
Nagakawa <i>et al.</i> , 2005 (10)	13/30	X	X	10 (33.3)	5 (16.7)	X	X	4 (13.3)	X	X	1 (3.3)	3 (10)	X	X	X	X	X	X
Yamamoto <i>et al.</i> , 1999 (11)	23/51	X	X	19 (37.2)	10 (19.6)	4 (7.8)	8 (15.6)	X	1 (1.9)	X	3 (5.8)	3 (5.8)	X	X	X	X	X	X
Guglielmi <i>et al.</i> , 2013 (12)	18/54	X	X	18 (33.3)	1 (1.8)	3 (5.5)	4 (7.4)	1 (1.8)	0	0	X	1 (1.8)	X	X	X	X	X	X
Jiang <i>et al.</i> , 2010 (13)	84/90	X	X	X	X	6 (6.6)	29 (32.2)	X	X	X	X	X	X	X	X	55 (61.1)	X	X
Chen <i>et al.</i> , 2011 (14)	76/320	54 (16.8)	X	X	X	5 (1.5)	17 (5.3)	X	X	X	X	X	X	X	X	X	X	X
No. of patients/total	54/320	54/320	X	67/174	28/174	29/554	65/554	11/123	6/144	5/93	7/120	8/174	X	X	55/90	X	X	
Pooled rate	52.3%	16.9	X	38.7	17.0	7.0	13.5	10.1	4.0	4.8	6.1	5.5	X	X	61.1	X	X	
95% CI	30.2-73.6	13.2-21.4	X	31.0-47.0	8.2-31.9	2.3-19.2	5.7-28.8	3.9-23.6	0.7-19.8	0.4-41.6	2.9-12.2	2.8-10.7	X	X	50.7-70.6	X	X	

CI: Confidence interval; HI: hilar; PD: pancreaticoduodenal anterior and posterior; HD: along hepatoduodenal ligament; CHA: common hepatic artery; PA: para-aortic; RP: retropancreatic; LG: along left gastric artery; SMA: along superior mesenteric artery; CE: along celiac artery; LC: along the lesser gastric curvature; CA: cardiac; CD: along the cystic duct; PC: pericholedochal; RPR: retroportal; SA: along the splenic artery; PI: pancreatic inferior; SI: splenic hilum; X: station not reported.

Table III. Distribution of lymph node involvement (LNI) in extrahepatic biliary tract carcinoma.

Author, year (Ref no.)	No. patients with LNI/total patients	Location of LNI, number of patients (%)															
		HI	PD	HD	CHA	PA	RP	LG	SMA	CE	LC	CA	CD	PC	RPR	SA	PI
Guglielmi <i>et al.</i> , 2013 (12)	30/72	X	X	30 (41.6)	8 (11.1)	0	5 (6.9)	4 (5.5)	0	0	X	0	X	X	X	X	X
Yoshida <i>et al.</i> , 1999 (15)	25/42	X	20 (47.6)	17 (40.4)	6 (14.2)	6 (14.2)	X	0	6 (14.2)	0	X	X	X	X	0	X	X
Yoshida <i>et al.</i> , 1998 (16)	11/20	X	7 (35)	7 (35)	6 (30)	5 (25)	X	X	X	X	X	X	X	X	X	X	X
Kitagawa <i>et al.</i> , 2001 (17)	58/110	X	16 (14.5)	X	30 (27.2)	19 (17.2)	X	X	4 (3.6)	7 (6.3)	X	X	X	X	47 (42.7)	34 (30.9)	X
No. of patients/total	43/172	54/134	50/244	30/172	5/72	4/114	6/114	7/224	X	0/72	X	47/110	34/110	0/42	X	X	
Pooled rate	51.0%	30.1	40.3	19.7	15.2	6.9	5.6	4.9	2.8	X	0	X	42.7	30.9	0	X	
95%CI	43.5-58.5	12.2-57.1	132.4-48.8	11.8-31.0	8.0-27.0	2.9-15.6	2.1-13.9	1.2-18.5	0.6-11.9	X	0	X	33.8-52.1	23.0-40.1	X	X	

CI: Confidence interval; HI: hilar; PD: pancreaticoduodenal anterior and posterior; HD: along hepatoduodenal ligament; CHA: common hepatic artery; PA: para-aortic; RP: retropancreatic; LG: along left gastric artery; SMA: along superior mesenteric artery; CE: along celiac artery; LC: along the lesser gastric curvature; CA: cardiac; CD: along the cystic duct; PC: pericholedochal; RPR: retroportal; SA: along the splenic artery; PI: pancreatic inferior; SI: splenic hilum; X: station not reported.

Table IV. Distribution of lymph node involvement (LNI) in gallbladder carcinoma.

Author, year (Ref no.)	No. patients with LNI/total patients	Patients with LNI, n (%)															
		HI	PD	HD	CHA	PA	RP	LG	SMA	CE	LC	CA	CD	PC	RPR	SA	PI
Negi <i>et al.</i> , 2011 (18)	33/57	X	X	X	11 (19)	X	7 (13)	X	X	X	X	13 (24)	14 (25)	11 (19)	X	X	X
Kondo <i>et al.</i> , 2002 (19)	66/112	X	X	15 (13.4)	X	32 (45.5)	X	X	X	X	X	X	X	X	X	X	X
Liu <i>et al.</i> , 2013 (20)	37/78	4 (5.1)	6 (7.6)	X	10 (12.8)	0	X	0	1 (1.2)	X	X	18 (23)	20 (25.6)	12 (15.3)	X	X	X
Total (no. patients/total)	4/78	6/78	15/112	21/135	32/190	7/57	X	0/78	1/78	X	X	31/135	34/135	23/135	X	X	X
Pooled rate	54.9	5.1	7.7	13.4	15.8	6.0	X	0	1.3	X	X	23.0	25.2	17.1	X	X	X
95% CI	47.6-62.1	1.9-12.9	3.5-16.1	8.2-21.0	10.3-23.2	1.0-78.3	6.0-23.6	0	0.2-8.5	X	X	16.6-30.8	18.6-33.2	11.6-24.5	X	X	X

CI: Confidence interval; HI: hilar; PD: pancreaticoduodenal anterior and posterior; HD: along hepatoduodenal ligament; CHA: common hepatic artery; PA: para-aortic; RP: retropancreatic; LG: along left gastric artery; SMA: along superior mesenteric artery; CE: along celiac artery; LC: along the lesser gastric curvature; CA: cardiac; CD: along the cystic duct; PC: pericholedochal; RPR: retroportal; SA: along the splenic artery; PI: pancreatic inferior; SI: splenic hilum; X: station not reported.

Recommendations for target definition. Details on the rates of lymph node station involvement in patients with intra-, extrahepatic and gallbladder neoplasms are reported in Tables II, III and IV, respectively. Based on these estimates, Table V reports the lymph node stations that should be included in delineation of nodal target volume according to the tumour location.

Intrahepatic biliary cancer. The following lymph node stations should be included in the target volume: retroportal (frequency=61.1%, 95% CI=50.7-70.6%), those along the hepatoduodenal ligament (38.7%, 95% CI=31.0-47.0%), along the common hepatic artery (17.0%, 95% CI=8.2-31.9%), hilar lymph nodes (16.9%, 95% CI=13.2-21.4%), retropancreatic (13.5%, 95% CI=5.7-28.8%), left gastric artery (10.1%, 95% CI=3.9-23.6%), para-aortic (7.0%, 95% CI=2.3-19.2%), lesser gastric curvature (6.1%, 95% CI=2.9-12.2%) and cardiac nodes (5.5%, 95% CI=2.8-10.7%). Celiac trunk and nodes along superior mesenteric artery lymph nodes should be excluded from the target volume because they were found to be involved in fewer than 5% of cases.

Extrahepatic biliary cancer. The following lymph node stations should be included in the target volume: pericoledochal (frequency=42.7%, 95% CI=33.8-52.1%), those along the hepatoduodenal ligament (40.3%, 95% CI=32.4-48.8%), retroportal lymph nodes (30.9%, 95% CI=23.0-40.1%), pancreatico-duodenal anterior and posterior (30.1%, 95% CI=12.2-57.1%), along the common hepatic artery (19.7%, 95% CI=11.8-31.0%), para-aortic (15.2%, 95% CI=8.0-27.0%), retropancreatic (6.9%, 95% CI=2.9-15.6%) and those along the left gastric artery (5.6%, 95% CI=2.1-13.9%). Celiac trunk and nodes along superior mesenteric artery lymph nodes should be excluded from the target volume because they were found to be involved in fewer than 5% of cases.

Gallbladder cancer. The following lymph node stations should be included in the target volume: pericoledochal (frequency=25.2%, 95% CI=18.6-33.2%), along cystic duct (23.0%, 95% CI=16.6-30.8%), retroportal lymph nodes (17.1%, 95% CI=11.6-24.5%), along the common hepatic artery (15.8%, 95% CI=10.3-23.2%) and those along the hepatoduodenal ligament (13.4%, 95% CI=8.2-21.0%), retropancreatic (12.3%, 95% CI=6.0-23.6%), pancreatic-duodenal anterior and posterior (7.7%, 95% CI=3.5-16.1%), para-aortic (6.0%, 95% CI=1.0-78.3%) and hilar lymph nodes (5.1%, 95% CI=1.9-12.9%).

Discussion

Surgical resection remains the most important treatment for patients with BTC, but despite improvements in surgical techniques and adjuvant treatments, resected biliary

Table V. Lymph node stations to be included or excluded in delineation of nodal target volume according to tumour location.

Tumour location	Lymph node station																
	HI	PD	HD	CHA	PA	RP	LG	SMA	CE	LC	CA	CD	PC	RPR	SA	PI	SI
IHBT	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	N	Y	N	N	N
EHBT	N	Y	Y	Y	Y	Y	Y	N	N	N	N	N	Y	Y	N	N	N
GB	Y	Y	Y	Y	Y	Y	N	N	N	N	N	Y	Y	Y	N	N	N

IHBT: Intrahepatic biliary tract; EHBT: intrahepatic biliary tract; GB: gallbladder; Y: Yes; N: No; HI: hilar; PD: pancreaticoduodenal anterior and posterior; HD: along hepatoduodenal ligament; CHA: common hepatic artery; PA: para-aortic; RP: retropancreatic; LG: along left gastric artery; SMA: along superior mesenteric artery; CE: along celiac artery; LC: along the lesser gastric curvature; CA: cardiac; CD: along the cystic duct; PC: pericholedochal; RPR: retroportal; SA: along the splenic artery; PI: pancreatic inferior; SI: splenic hilum.

neoplasms still locally recur at a high rate, and in patients not suitable for resection, local progression represents the main cause of death (21). Park and colleagues showed that more than 60% of patients with resected extrahepatic biliary cancer had locoregional recurrence (22). Jung and co-workers reported even higher locoregional recurrence rates, of 70%, 86%, and 57%, in patients with gallbladder, intrahepatic, and extrahepatic cancer, respectively (23).

Several retrospective studies have shown that chemoradiation can improve local control and overall survival in selected patients in both adjuvant and neo-adjuvant settings (3-5). Unfortunately, these data derived from retrospective series and therefore future prospective randomized trials are necessary to confirm these results. In the past, radiotherapy of abdominal tumors was limited by the tolerance of organs at risk. IMRT technique and image-guided radiation therapy can deliver radiation doses to the target while sparing surrounding organs. Thus, these emerging techniques are expanding the treatment of BTC. Recently, it was shown that IMRT of BTC achieved safe dose escalation without dose-limiting toxicity (24). With the advent of these new techniques, the accurate definition of the tumour target volume and of draining lymph nodal areas that should be prophylactically irradiated is crucial. Standardized guidelines for target definition for prophylactic nodal irradiation are currently lacking.

Areas at higher risk for local relapse are generically identified as nodes along the porta hepatis, pancreaticoduodenal system and celiac axis, however no specific indications in published literature are available. Therefore, our systematic review was performed in order to identify the lymph node stations mainly involved according to primary tumour location and to provide a practical tool for radiotherapists for target volume delineation.

Interestingly, the study of Guglielmi *et al.* found that the most frequently involved lymph node station, in both intrahepatic and extrahepatic tumour locations, was along the

lymph nodes of the hepatoduodenal ligament (12). Moreover, all patients with positive lymph nodes in other regions (such as cardiac and celiac trunk, along gastric artery, common hepatic artery, pancreaticoduodenal and along superior mesenteric artery lymph nodes) always had involvement of the hepatoduodenal ligament lymph node station. Therefore, since this station does not appear to be 'skipped' during the metastatic process, it should be considered an obligatory step.

Our study has certain limitations. Despite our data being derived from surgical series, sampling of all the lymph node stations was not always performed, therefore our information is partially incomplete. Furthermore, we were unable to give indications about which lymph node stations should be included in the target volume based on the different extrahepatic subsites (*i.e.* Klatskin or distal choledochal neoplasms) because these kind of data were lacking. Moreover, our findings cannot suggest target modulation based on clinical tumour and nodal stages. The chosen cut-off (5%) for inclusion in the target may seem rather low. However, our study addresses even advanced tumors, in which the incidence of nodal metastasis is probably higher than the incidence reported in surgical series, obviously including less advanced cancer.

This systematic review was based on pathological studies in patients who underwent resection, but more information could come from studies of patterns of failure aimed at analyzing the sites of relapse of primary tumour and nodal stations after radiochemotherapy, using systematic imaging monitoring.

In conclusion, we have proposed an evidence-based nodal target definition in BTC based on the site of primary tumor (namely intrahepatic, extrahepatic or gallbladder) that could represent a practical and useful tool for radiotherapists.

Conflicts of Interest

No actual or potential conflicts of interest exist regarding this article.

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