Caudate Lobectomy for Perihilar Cholangiocarcinoma – Current Evidence

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Rezumat

Rezecția de lob caudat în colangiocarcinoamele perihilare – status actual

Chirurgia reprezintă singura șansă de supraviețuire pe termen lung pentru pacienții diagnosticați cu colangiocarcinom perihilar. Rezecția cu viză curativă a cunoscut de-a lungul anilor îmbunătățiri semnificative, pornind de la rezecția doar a căii biliare principale și ajungând la proceduri chirurgicale complexe ce includ limfodisecția loco-regională, rezecții hepatice majore și, uneori, rezecții vasculare asociate. Acest tip modern de abord chirurgical a dus la îmbunătățirea substanțială a supraviețuirii acestor pacienți, în pofida unei rate mari de complicații postoperatorii. În Europa și America, rezultatele inițiale ale acestui tip complex de abord chirurgical incluzând rezecții hepatice majore au fost dezamăgitoare deoarece s-au asociat cu rate ale mortalității postoperatorii inacceptabil de mari. Astăzi, mortalitatea după rezecția colangiocarcinoamelor perihilare a scăzut semnificativ, dar totuși rata mortalității în centrele din Europa și America rămâne mai mare decât rata raportată în centrele din Estul Asiei. Aceste diferențe de rezultate între centrele din Europa – America și Estul Asiei nu sunt explicate doar prin diferențele de abord terapeutic dar și de caracteristicile diferite ale pacienților din cele două părți ale lumii. Rezecția în bloc a lobului caudat ca parte a rezecțiilor radicale pentru colangiocarcinoame perihilare a fost introdusă în practica clinică de mai bine de trei decenii. Susținerea rezecției de lob caudat se bazează pe modalitatea de răspandire locală a acestui tip de tumori precum și pe faptul că invazia de lob caudat este un fapt frecvent întâlnit în acest tip de tumori. Rezecția de lob

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caudat ca parte a chirurgiei cu viză curativă a colangiocarcinoamelor perihilare a fost abordată într-o serie de articole din literatură, dar, totuși, concluziile acestor studii nu au fost relevante în ceea ce privește impactul acestei proceduri chirurgicale. Scopul acestei lucrări este acela de a face o trecere în revistă a literaturii de specialitate care analizează rolul și impactul rezecției de lob caudat în colangiocarcinoamele perihilare.

Cuvinte cheie: rezecție de lob caudat, colangiocarcinom perihilar, margini de rezecție, morbiditate, recidivă, supraviețuire

Abstract

At the moment, surgery is considered the only therapeutic approach offering a chance of long-term survival in patients diagnosed with perihilar cholangiocarcinoma (PHC). Curative intent surgery for PHC has experienced significant technical improvements over the years, from simple bile duct resection to complex surgical procedures including lymph nodes dissection, major hepatectomies and, sometimes, vascular resections. The modern surgical approach of PHC is associated with significantly improved survival rates, albeit with increased postoperative morbidity. The initial Western experience with major hepatectomies for PHC was not encouraging, as it was associated with unacceptably high mortality rates. Currently the mortality rates after surgery for PHC have significantly decreased, but it appears that the mortality rates in Western centres still remain higher, compared with the East Asian centres. The differences of outcomes between East Asian and Western centres are explained not only by the management of PHC but also by patient characteristics. En bloc caudate lobectomy as part of radical resections for PHC has been reported in clinical practice nearly three decades ago. The rationale of en bloc caudate lobectomy is based on the pattern of tumour spread in PHC, taking in consideration the fact that caudate lobe invasion appears to be a frequent event in patients resected for PHC. While en bloc caudate lobectomy in the context of curative intent surgery for PHC has been discussed in a host of publications so far, the currently available literature reached conflicting results regarding its overall impact on the patient. Therefore, the aim of this paper is to review the current relevant literature pertaining to the impact of en bloc caudate lobectomy in the context of curative intent surgery for PHC.

Key words: caudate lobectomy, perihilar cholangiocarcinoma, resection margins status, morbidity, recurrence, survival

Introduction

Perihilar cholangiocarcinoma (PHC) is defined as cholangiocarcinoma involving the hilar bile duct (i.e., the duct located topologically between the right side of the umbilical portion of the left portal vein and the left side of the origin of the right posterior portal vein), and it was proven to be a clinically valid concept (1). Historically, it was Dr. Gerald Klatskin who first described in details this type of tumour in 1965 (2).

PHC carries a poor prognosis (3) and surgery

is at the moment the best treatment and the only chance for long-term survival in patients diagnosed with PHC (3,4). However, only a minority of patients (around 25%) with PHC are amenable to resection at the time of diagnosis (3).

Curative intent surgical techniques for PHC have significantly changed over the years, evolving from simple bile duct resection to complex surgical procedures including lymph nodes dissection, major hepatectomies (5-7) and, sometimes, even vascular resections

(5,7,8). Recently, liver transplantation has emerged as the treatment choice in selected patients with PHC, with excellent outcomes (9). In highly experienced hands, minimally invasive liver resection for PHC has been demonstrated to be safe and feasible (10).

The initial Western experience with major hepatectomies for PHC was not encouraging, as it was associated with unacceptably high mortality rates (up to 27% of patients)(11,12). Only few Western centres reported good outcomes with aggressive surgical approaches for PHC before the year 2000 (13,14). Currently the mortality rates after surgery for PHC have significantly decreased, but it appears that the mortality rates in Western centres still remain higher, compared with the East Asian centres (6,7,15). The differences of outcomes between East Asian and Western centres are explained not only by the management of PHC but also by patient characteristics (16).

The modern surgical approach of PHC is associated with significantly improved survival rates but the morbidity rates remain high even in high-volume centres (7). Furthermore, high postoperative mortality rates after aggressive surgery for PHC should be a cause for caution. Recent reviews have shown that in high-volume centres the morbidity and mortality rates after curative intent surgery for PHC vary between 6% - 73% and 0% - 15%, respectively, while the 5-year survival rates vary between 13% - 44% (6,7). Postoperative bile leak and liver failure are the most frequent postoperative complications after resection for PHC, and liver failure is considered the main cause of postoperative mortality(15,17). Pre-operative optimization including portal vein embolization and biliary decompression are considered key factors for improved outcomes of surgery for PHC (5,17,18).

En bloc caudate lobectomy as part of radical resections for PHC has been reported in clinical practice nearly three decades ago (19). The rationale of en bloc caudate lobectomy is based on the pattern of tumour spread in PHC (20), taking in consideration the fact that caudate lobe invasion appears to

be a frequent event in patients resected for PHC (22.2% - 42.3% of cases)(19,21,22). Moreover, few studies have identified caudate lobe invasion as a potential risk factor for both disease-free and overall survival (21,22).

Currently there is a wide consensus regarding the inclusion of en bloc caudate lobectomy as a mandatory component of curative intent surgery for PHC (6), in order to achieve improved control of local tumour extent. The potential benefits of adding en bloc caudate lobectomy to surgical resections for PHC are increased rates of negative resection margins, decreased local recurrence rates and improved survival (23). However, it is important to note that due to its particularly profound anatomical location, between the inferior vena cava and hepatic hilum, caudate lobectomy can be challenging and may potentially increase the operative complications rate.

The aim of this paper is to review the current relevant literature pertaining to the role and the impact of en bloc caudate lobectomy in the surgery for PHC.

Literature Search

A systematic literature search was performed in the PubMed-Medline database using the terms “hilar cholangiocarcinoma” and “Klatskin tumor”. Relevant studies providing data about the role and impact of en bloc caudate lobectomy in curative intent surgery for PHC have been extracted and further analyzed. The endpoints assessed for this procedure were resection margin status, recurrence rates, as well as early and late outcomes.

Caudate Lobe Anatomy – Implications in PHC Surgery

The anatomy of the hilar area and its connections with the caudate lobe has been investigated in several studies, with a particular emphasis on the implications of PHC surgery (19,24-31).

The caudate lobe occupies the space below the hepatic hilum, in close proximity to the

biliary ductal confluence and the portal and hepatic artery bifurcations (24,25). Several classifications of caudate lobe subdivisions have been described (24,27). The most useful segmentation of the caudate lobe from a clinically practical standpoint includes the Spiegel lobe (left subsegment), the caudate process (right subsegment) and the paracaval portion (medial subsegment) (24,27).

According to the Brisbane classification, the caudate lobe (i.e., segment 1) should be differentiated from segment 9, based on internal anatomy (32). Thus, segments 1 and 9 constitute the dorsal sector in the Couinaud anatomy (33), but this term is no longer accepted by the Brisbane classification (32). The caudate lobe (i.e., segment 1) is defined as a protuberance which comprises also the tissue uniting the segment anteriorly to the liver and lies to the left and in front of the inferior vena cava, while segment 9 is completely incorporated in the posterior surface of the liver and lies in front and to the right of the inferior vena cava (33). The two segments are united inferiorly by the caudate process (33) (Figs. 1, 2).

Embryologically, the caudate lobe develops separately from the main liver and displays abundant vascular connections with the hepatic veins, inferior vena cava and portal veins (24,26). Some authors suggest the caudate lobe might develop from both hepatic lobes (25).

The caudate lobe portal supply possesses a large variability, and is provided by one to six branches that may arise from either the left and/or the right portal branches or from the portal vein bifurcation (24,26-29). However, it appears that there is a left-sided predominance of portal supply of the caudate lobe (26). Careful identification and ligation of these branches during caudate lobectomy are mandatory in order to avoid hemorrhagic complications, particularly when the size of these branches is non-negligible. Preoperative identification of such branches with imaging methods may potentially guide the caudate lobectomy, as well as intraoperative ultrasound (34).

Figure 1. Caudate lobe (segment 1) relationships with the surrounding structures (Sg.1 – segment 1; Sg. 9 – segment 9; IVC – inferior vena cava; PV – portal vein; RPP – right portal pedicle; RPGP – right posterior glissonian pedicle; LPP – left portal pedicle; RHV – right hepatic vein; MHV – middle hepatic vein; LHV – left hepatic vein; AL – Arantius ligament) (modified from (70), with permission)

Figure 2. Glissonian pedicles for segments 1 and 9 (I – segment 1; IX – segment 9; IVC – inferior vena cava; PV – portal vein; RPP – right portal pedicle; RPGP – right posterior glissonian pedicle; LPP – left portal pedicle; RHV – right hepatic vein; MHV – middle hepatic vein; LHV – left hepatic vein; AL – Arantius ligament; HA – hepatic artery; CBD – common bile duct) (modified from (70), with permission)

Both the arterial supply of the caudate lobe as well as its biliary drainage are also highly variable (24,26-29). The caudate lobe is drained by an average of four bile ducts (26,27). A dominant left biliary branch is often recognized during surgery and ligated, but branches to the hilum or right bile duct may also occur (24,28). This substantial variability in the anatomy of biliary drainage of the caudate lobe might explain the local spread of PHC towards this structure (24,26,31). Careful identification of small bile ducts from the caudate lobe may help in the prevention of postoperative bile leaks, which represent a frequent complication after PHC resections.

A study performed in Nagoya has shown that certain bile duct abnormalities of the caudate lobe (e.g. infraportal bile duct) may create difficulties during right hemi-hepatectomies for PHC (30).

The venous outflow of the caudate lobe consists of several small veins that drain directly into the inferior vena cava, as well as in the left and middle hepatic veins (24,26,28).

In summary, the knowledge of caudate lobe anatomy is of utmost importance for liver surgeons and may have oncological implications, especially in patients with PHC. Due to close connections to the bile duct hilum, a PHC can easily spread into the caudate lobe. Therefore, routine en bloc caudate lobectomy in these patients appears to be anatomically justified (*Fig. 3*).

Figure 3. Types of approach for en bloc caudate lobectomy (segment 1 resection) (I – segment 1; IX – segment 9; VII – segment 7; IVC – inferior vena cava; RHV – right hepatic vein; MHV – middle hepatic vein) (modified from(70), with permission)

Caudate Lobectomy – How Frequent is it Used in Surgery for PHC?

The importance of tumour involvement of the caudate lobe and the benefits of routine en bloc caudate lobectomy as part of curative intent surgery for PHC has been suggested for many years by the Japanese surgical teams (19,35-37). However, Western centres were quite slow in adopting routine caudate lobectomy for PHC patients (38-41). Noteworthy, few Western centres included en bloc caudate lobectomy in curative intent surgery for PHC in an early setting (13,42).

A study comparing the surgical practice and outcomes between a Western centre (Lahey, USA) and an East Asian centre (Nagoya, Japan) revealed significant differences (23). Strikingly, in the Lahey cohort only 8% of patients underwent caudate lobectomy, compared to 89% in the Nagoya series (23). The study has clearly shown that liver resection including caudate lobectomy has been associated with increased resectability and negative resection margins rates, as well as improved overall survival (23).

After the results of the aforementioned study were published (23), en bloc caudate lobectomy was adopted on a far larger scale in most surgical centres as part of surgery for PHC, including Western centres (12,22). At the moment it appears that the differences in terms of surgical approach and outcomes between East Asia and Western centres are starting to be mitigated (43).

A review paper published in 2015 has shown that the rate of en bloc caudate lobectomy in PHC in series published between 1990 and 2013 varied between 15% and 100% (7). Increasing rates of caudate lobectomy were reported in large series of curative intent surgery for PHC published in the last 5 years: 35.3% – 100%. The adoption rate of en bloc caudate lobectomy appears to remain higher in East Asian surgical centres, compared to Western centres (7,21,43-55).

Few surgical teams have introduced the concept of hilar en bloc resection for the treatment of PHC (13,42). This concept implies

an extended hepatectomy (i.e., right trisectionectomy), en bloc caudate lobectomy and combined portal vein resection in principle (13,42). This kind of approach has been associated with increased rates of negative resection margins, improved survivals and no added morbidity, compared to the standard major hepatectomies for PHC (13,42).

In summary, en bloc caudate lobectomy has gained wide acceptance as part of curative intent surgery for PHC all over the world. However, geographical disparities between Western and East Asian surgical centres still exist.

Caudate Lobectomy and Resection Margins Status in PHC

Negative resection margins and absence of lymph node metastases are widely considered the main prognostic factors after curative intent surgery for PHC (6,7). Furthermore, proximal resection margins (toward the caudate lobe) appear to have a more relevant prognostic role, compared to the distal resection margins (56). Consequently, achieving negative resection margins is of utmost importance in patients with surgery for PHC (6) and en bloc caudate lobectomy may potentially play a significant role.

The negative resection margins rates reported in large series from literature of resected patients with PHC vary between 14% and 95% (7).

Many studies associated en bloc caudate lobectomy with increased negative resection margins rates after curative intent surgery for PHC (12,23,44,55,57-59)(Table 1), while others did not (60).

In summary, most studies in the current literature associate en bloc caudate lobectomy with increased negative resection margins rates after curative intent surgery for PHC.

Caudate Lobectomy and Postoperative Complications in PHC

Morbidity rates after curative intent surgery for PHC are widely considered to be high even

in high-volume centres (7,15,17).

The majority of the studies available so far found no positive correlation between en bloc caudate lobectomy and increased rates of postoperative complications after surgery for PHC (22,23,44,57,59-61)(Table 1). However, few studies showed increased morbidity rates when caudate lobectomy is performed as part of surgery for PHC (62).

Some experienced surgical teams suggested that caudate lobectomy may reduce the risk of bile leak after right trisectionectomy (42).

Our previous studies have explored the potential impact of en bloc caudate lobectomy on postoperative complications after surgery for PHC (15). Caudate lobectomy was not found to be associated with increased risk of severe complications or clinically relevant postoperative bile leak, liver failure or haemorrhage rates (15).

In summary, most studies in the current literature did not associate en bloc caudate lobectomy with increased morbidity rates after curative intent surgery for PHC.

Caudate Lobectomy and Recurrence in PHC

Recurrence is widely considered a frequent event [44% - 68% (63-65)] after curative intent surgery for PHC.

While several studies did not show any impact of en bloc caudate lobectomy on recurrence rates after curative intent surgery for PHC (44,60,66), others associated caudate lobectomy with decreased recurrence rates (51,59,65,67) (Table 1).

Our previous studies did not identify any correlation of en bloc caudate lobectomy with disease-free survival in patients resected for PHC (21).

In summary, the association of en bloc caudate lobectomy with decreased recurrence rates after curative intent surgery for PHC has been approached in some studies, however the topic remains controversial.

Caudate Lobectomy and Long-Term Survival in PHC

Several studies associated en bloc caudate

Table 1. Studies of the literature comparing morbi-mortality, negative resection margins, recurrence and overall survival rates of patients with and without en bloc caudate lobectomy for perihilar cholangiocarcinomas

Caudate lobectomy (Yes vs. No)	Kow (60), 2012	Wahab (59), 2012	Cheng (57), 2012	Bhutiani (44), 2018
No of patients	70 vs. 57	80 vs. 79	137 vs. 34	90 vs. 166
Negative resection margins rate	91.4% vs. 84.2%	71.2% vs. 38%	89% vs. 35% ^a	76% vs. 60% ^a
Morbidity rate	4.3% vs. 8.8%	53.8% vs. 50.6%	28% vs. 21%	59% vs. 66%
Mortality rate	1.4% vs. 3.5%	8.8% vs. 3.8%	2.9% vs. 2.9%	10% vs. 14%
Recurrence rate	37.1% vs. 42.1%	51.3% vs. 67.1% ^a	NA	NA
Median overall survival	64 vs. 34.6 months ^a	36 vs. 22 months ^a	30 vs. 17 months ^a	37.4 vs. 32.2 months ¹

^aP values < 0.05; ¹mean; NA – not available

lobectomy with increased overall survival rates after curative intent surgery for PHC (23,55,57,59,60,67) (Table 1), while others did not (22,44,46,47,52,58,66,68).

Our previous studies did not identify any correlation between en bloc caudate lobectomy and overall survival in patients resected for PHC (21).

In summary, the association of en bloc caudate lobectomy with improved survival rates after curative intent surgery for PHC remains to be demonstrated.

The Role of Caudate Lobectomy in PHC – What is the Level of Evidence?

Current studies of the literature regarding the role and impact of en bloc caudate lobectomy in PHC are providing low levels of evidence-based medicine. Thus, there are no randomized studies. Furthermore, most studies have a retrospective design (12,15,21-23,44,46,51,52, 55,57-62,65-68) and only four studies are comparative, un-matched studies (44,57,59,60) (Table 1). There is also evidence coming from an expert opinion (42).

However, it is noteworthy mentioning that a systematic review and meta-analysis about the role of en bloc caudate lobectomy in PHC has been recently published (69). This meta-analysis was performed on six retrospective studies comparing patients with major hepatectomies with either caudate lobectomy or not (69). The conclusion of the meta-analysis is that en bloc caudate lobectomy may improve the likelihood of negative resection margins

and overall survival rates in patients resected for PHC, without added morbidity (69). The paucity of data and the retrospective design of the included studies limit the results of this meta-analysis (69).

In summary, current literature provides low levels of evidence-based medicine regarding the role and impact of en bloc caudate lobectomy in PHC.

Conclusion

Nowadays, en bloc caudate lobectomy, although a challenging surgical procedure, has gained wide acceptance as a mandatory part of curative intent surgery for PHC all over the world, albeit geographical disparities between Western and East Asia surgical centres still exist.

The anatomical rationale for en bloc caudate lobectomy is represented by the proximity of the caudate lobe to hilar bile duct structures, and its corollary, the early spread of PHC in the caudate lobe.

Current relevant literature appears to associate en bloc caudate lobectomy with increased negative resection margins rates after curative intent surgery for PHC, without increased morbidity rates. However, the association of en bloc caudate lobectomy with decreased recurrence and increased overall survival rates remains controversial.

It is important to emphasize the fact that current literature provides low levels of evidence-based medicine regarding the role and impact of en bloc caudate lobectomy in PHC.

Author Contributions

The two authors equally contributed to this paper regarding the intellectual concept and design of the study, the literature review and analysis, as well as the drafting, critical revision, editing, and approval of the final version of the manuscript.

Conflict-of-Interest Statement

No potential conflicts-of-interest related to this article. No financial support.

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