Endoscopic and Photodynamic Therapy of Cholangiocarcinoma

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Keywords

Cholangiocarcinoma · Endoscopic therapy · Photodynamic therapy

Summary

Background: Most patients with cholangiocarcinoma (CCA) have unresectable disease. Endoscopic bile duct drainage is one of the major objectives of palliation of obstructive jaundice. **Methods/Results:** Stent implantation using endoscopic retrograde cholangiography is considered to be the standard technique. Unilateral versus bilateral stenting is associated with different advantages and disadvantages; however, a standard approach is still not defined. As there are various kinds of stents, there is an ongoing discussion on which stent to use in which situation. Palliation of obstructive jaundice can be augmented through the use of photodynamic therapy (PDT). Studies have shown a prolonged survival for the combinations of PDT and different stent applications as well as combinations of PDT and additional systemic chemotherapy. **Conclusion:** More well-designed studies are needed to better evaluate and standardize endoscopic treatment of unresectable CCA.

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Endoscopic Therapy of Cholangiocarcinoma

Endoscopic treatment of cholangiocarcinoma (CCA) with obstructive jaundice ensures bile duct drainage in preoperative or palliative settings and has been evaluated in a number of prospective and retrospective cohort studies. However, preoperative bile duct drainage in distal cholangiocarcinoma (dCCA) is not always necessary and might be associated with an increased risk of cholan-

gitis and postoperative infectious complications [1, 2]. Nevertheless, in the presence of acute cholangitis, sepsis, bilirubin > 10 mg/dl, scheduled neoadjuvant therapy, or the need of extensive hepatic resection, preoperative bile duct drainage should be ensured to reduce peri- and postoperative complications [3]. Liver segments that will remain after surgery should be drained sufficiently with a plastic stent to improve postoperative liver function and regeneration.

For unresectable CCA, endoscopic bile duct drainage is one of the major objectives of palliative treatment (fig. 1). Stent implantation using endoscopic retrograde cholangiography (ERC) should be considered as the standard procedure since same results and fewer complications can be expected when compared to percutaneous stent implantation or surgical creation of a biliodigestive anastomosis [4, 5]. There is an ongoing discussion whether bilateral drainage should be preferred over unilateral drainage in CCA arising from the biliary bifurcation. As drainage of 30% of the liver volume is considered to be sufficient to resolve jaundice [6], a single stent for the dominant liver segment may be adequate. In addition, a single stenting is technically easier and less expensive. On the contrary, injecting contrast medium into undrained ducts is associated with a higher risk of cholangitis [7]. In order to prevent this complication bilateral stenting might be required. Several reports have compared the outcomes of unilateral versus bilateral stenting for unresectable hilar CCA. In one retrospective study [8], the best survival rate was observed in patients with bilateral (plastic) stenting. Those patients with cholangiographic opacification of both lobes but drainage of only one lobe had the worst survival rates. Another retrospective study showed no differences between unilateral versus bilateral (metal) stenting [9]. A prospective controlled and randomized study showed no significant advantage for bilateral (plastic) stenting [10]. Moreover, the bilateral stenting group had a higher rate of early complications (such as early cholangitis) compared to the unilateral (plastic) stenting group. Another retrospective study showed similar results for metal stents as

Fig. 1. Biliary drainage via **a** plastic stents and **b** metal stents.

Fig. 2. **a** Photodynamic therapy (PDT) in the **b** left and **c** right hepatic duct. **d** ERC 10 days after PDT.

no differences between unilateral and bilateral stenting were observed (with respect to survival time, stent patency, complication-free survival), though with higher complication rates (liver abscess) in the bilateral stenting group [11]. In conclusion, it still remains unclear whether unilateral or bilateral stenting is superior in the endoscopic treatment of hilar CCA. Further well-designed studies are needed to clarify the best stenting approach for hilar CCA. Until then, initial unilateral stenting with additional stenting in cases of incomplete resolution of jaundice and cholangitis might be a reasonable strategy.

What Kind of Stent to Use in Which Situation?

The use of polyethylene stents and self-expanding metal stents (SEMS) in the treatment of biliary obstruction has been well investigated. Different types of stents are available; however, a systematic review concluded that neither stent type offered a survival advantage [12]. Plastic stents are less expensive but occlude by a me-

dian of 3–6 months because of the deposition of bacterial biofilm or tumor ingrowth [13]. Plastic stents are also associated with higher rates of stent migration. As a consequence, plastic stents need to be exchanged regularly. SEMS are more expensive, have a larger diameter, may be covered or uncovered, and have a low migration rate. For dCCA, SEMS have proven to be superior to plastic stents because they remain patent longer [14]. In the short term, metal stents are also superior to plastic stents in perihilar CCA (pCCA) because of lower rates for occlusion or reintervention [15]. Another possible advantage of SEMS in pCCA is the drainage of side branches of the biliary tract through the wire mesh. In the long term, the lack of removability of SEMS might pose problems if drainage becomes ineffective and stent revision is necessary. From an economic point of view, it has been suggested that the use of SEMS should be reserved for patients whose estimated survival is longer than 3–6 months [16, 17]. Ultimately, the endoscopic strategy for biliary drainage should be determined by the individual clinical situation, the locally available expertise, and the patient's preference.

Photodynamic and Systemic Therapy in Cholangiocarcinoma

In patients with unresectable CAA, palliation of obstructive jaundice can be augmented through the use of photodynamic therapy (PDT). After injection of a photosensitizing agent, laser stimulation of optical fibers (inserted by means of ERC) allows targeted tumor destruction in the bile ducts (fig. 2). Two meta-analyses showed significant improvements in biliary efflux, quality of life, and life expectation for PDT compared to stenting alone [18, 19]. The incidence of phototoxic reactions was approximately 11% in the study by Lu et al. [19]. A recently published study prospectively compared PDT (+ stenting, n = 12) with stenting alone (n = 27) and confirmed these findings. The 1-year survival rate was 58.3 versus 3.7%, with an average survival time of 13.8 versus 9.6 months [20]. Studies showed a prolonged overall survival in patients who received additional systemic chemotherapy compared to patients who were treated with PDT alone [21, 22]. In the study by Park et al. [21], oral fluoropyrimidine was evaluated in a prospective con-

trolled setting. The study by Wentrup et al. [22] evaluated different regimes (gemcitabine monotherapy or in combination with cisplatin, oxaliplatin, or capecitabine; 5-fluorouracil monotherapy or cisplatin plus irinotecan) in a retrospective setting.

Conclusion

Standard treatment of unresectable CCA is still not well researched. The combination of stenting, PDT, and systemic chemotherapy seems to be superior to stenting and PDT alone. More well-designed studies including different treatment modalities are needed to better define the optimal treatment at different time points in patients with unresectable CCA.

Disclosure Statement

Meier: none; Caca: none.

References

- 1 Hochwald SN, Burke EC, Jarnagin WR, Fong Y, Blumgart LH: Association of preoperative biliary stenting with increased postoperative infectious complications in proximal cholangiocarcinoma. *Arch Surg* 1999;134: 261–266.
- 2 Lai EC, Lau SH, Lau WY: The current status of preoperative biliary drainage for patients who receive pancreaticoduodenectomy for periampullary carcinoma: a comprehensive review. *Surgeon* 2014;12:290–296.
- 3 Iacono C, Ruzzenente A, Campagnaro T, Bortolasi L, Valdegamberi A, Guglielmi A: Role of preoperative biliary drainage in jaundiced patients who are candidates for pancreaticoduodenectomy or hepatic resection: highlights and drawbacks. *Ann Surg* 2013;257:191–204.
- 4 Andersen JR, Sorensen SM, Kruse A, Rokkjaer M, Matzen P: Randomised trial of endoscopic endoprosthesis versus operative bypass in malignant obstructive jaundice. *Gut* 1989;30:1132–1135.
- 5 Tibble JA, Cairns SR: Role of endoscopic endoprostheses in proximal malignant biliary obstruction. *J Hepatobiliary Pancreat Surg* 2001;8:118–123.
- 6 Larghi A, Tringali A, Lecca PG, Giordano M, Costamagna G: Management of hilar biliary strictures. *Am J Gastroenterol* 2008;103:458–473.
- 7 Yasuda I, Mukai T, Moriaki H: Unilateral versus bilateral endoscopic biliary stenting for malignant hilar biliary strictures. *Dig Endosc* 2013;25(suppl 2):81–85.
- 8 Chang WH, Kortan P, Haber GB: Outcome in patients with bifurcation tumors who undergo unilateral versus bilateral hepatic duct drainage. *Gastrointest Endosc* 1998;47:354–362.
- 9 Naitoh I, Ohara H, Nakazawa T, et al: Unilateral versus bilateral endoscopic metal stenting for malignant hilar biliary obstruction. *J Gastroenterol Hepatol* 2009;24: 552–557.
- 10 De Palma GD, Galloro G, Siciliano S, Iovino P, Catanzano C: Unilateral versus bilateral endoscopic hepatic duct drainage in patients with malignant hilar biliary obstruction: results of a prospective, randomized, and controlled study. *Gastrointest Endosc* 2001;53:547–553.
- 11 Iwano H, Ryoza S, Ishigaki N, et al: Unilateral versus bilateral drainage using self-expandable metallic stent for unresectable hilar biliary obstruction. *Dig Endosc* 2011;23:43–48.
- 12 Levy MJ, Baron TH, Gostout CJ, Petersen BT, Farnell MB: Palliation of malignant extrahepatic biliary obstruction with plastic versus expandable metal stents: an evidence-based approach. *Clin Gastroenterol Hepatol* 2004;2:273–285.
- 13 Baron TH: Palliation of malignant obstructive jaundice. *Gastroenterol Clin North Am* 2006;35:101–112.
- 14 Davids PH, Groen AK, Rauws EA, Tytgat GN, Huijbregtse K: Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. *Lancet* 1992;340:1488–1492.
- 15 Mukai T, Yasuda I, Nakashima M, et al: Metallic stents are more efficacious than plastic stents in unresectable malignant hilar biliary strictures: a randomized controlled trial. *J Hepatobiliary Pancreat Sci* 2013;20:214–222.
- 16 Kaassis M, Boyer J, Dumas R, et al: Plastic or metal stents for malignant stricture of the common bile duct? Results of a randomized prospective study. *Gastrointest Endosc* 2003;57:178–182.
- 17 Yeoh KG, Zimmerman MJ, Cunningham JT, Cotton PB: Comparative costs of metal versus plastic biliary stent strategies for malignant obstructive jaundice by decision analysis. *Gastrointest Endosc* 1999;49:466–471.
- 18 Leggett CL, Gorospe EC, Murad MH, Montori VM, Baron TH, Wang KK: Photodynamic therapy for unresectable cholangiocarcinoma: a comparative effectiveness systematic review and meta-analyses. *Photodiagnosis Photodyn Ther* 2012;9:189–195.
- 19 Lu Y, Liu L, Wu JC, Bie LK, Gong B: Efficacy and safety of photodynamic therapy for unresectable cholangiocarcinoma: a meta-analysis. *Clin Res Hepatol Gastroenterol* 2015;39:718–724.
- 20 Yang J, Shen H, Jin H, Lou Q, Zhang X: Treatment of unresectable extrahepatic cholangiocarcinoma using hematoporphyrin photodynamic therapy: a prospective study. *Photodiagnosis Photodyn Ther* 2016;DOI: 10.1016/j.pdpdt.2016.10.001.
- 21 Park DH, Lee SS, Park SE, et al: Randomised phase II trial of photodynamic therapy plus oral fluoropyrimidine, S-1, versus photodynamic therapy alone for unresectable hilar cholangiocarcinoma. *Eur J Cancer* 2014;50:1259–1268.
- 22 Wentrup R, Winkelmann N, Mitroshkin A, et al: Photodynamic therapy plus chemotherapy compared with photodynamic therapy alone in hilar nonresectable cholangiocarcinoma. *Gut Liver* 2016;10:470–475.