Impact of Neoadjuvant Chemotherapy on Hypertrophy of the Future Liver Remnant after Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy

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BACKGROUND: Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been demonstrated as a feasible procedure in extended liver resections as a means of successfully increasing the volume of the future liver remnant (FLR). Neoadjuvant chemotherapy (CTx) is toxic to the organ and may impair hepatic regeneration. This study was performed to assess the procedure's effect on hypertrophy of the FLR, including the short-term survival.

STUDY DESIGN: We analyzed 19 consecutive ALPPS patients, of whom 58% (n = 11) received neoadjuvant CTx because of colorectal liver metastasis (CRM). Patients presented with multifocal CRM (n = 11, 58%); cholangiocarcinoma (n = 7, 37%), of which 5 were in the Klatskin position; and gallbladder carcinoma (n = 1, 5%). Hepatectomy was performed within 6 to 13 days after hepatic partition. Volumetry was performed before both liver partitioning and hepatectomy. A survival analysis was performed.

RESULTS: Liver partition and portal vein ligation induced sufficient hypertrophy of the FLR, with an increased volume of 74% ± 35%. Patients underwent hepatectomy after a median of 8 days; in all cases R0 resection was achieved. Neoadjuvant CTx was shown to significantly impair hypertrophy. The volume of the FLR in non-CTx patients increased by 98% ± 35%; an increase of 59% ± 22% was observed in patients who underwent CTx ($p = 0.027$). Chemotherapy did not have an impact on either morbidity or in-hospital mortality, which were 68% and 16%, respectively. One-year overall survival was 53%, with a 1-year survival of 67% in CRM patients and 38% in non-CRM patients ($p > 0.05$).

CONCLUSIONS: Data presented here demonstrate for the first time that neoadjuvant CTx significantly impairs hypertrophy of the FLR after ALPPS. (J Am Coll Surg 2015;221:717−728. © 2015 by the American College of Surgeons)

Resection of hepatic primary and metastatic tumors remains the only curative treatment.[1-4] However, in order to achieve complete removal of all lesions, major primary or staged liver resections are often required.[4] Patient recovery after major hepatic surgery is influenced primarily by both the quality and volume of the liver remnant.[5] In fact, extended resection can result in small-for-size syndrome, with a heightened risk of post-hepatectomy liver failure.[6] For this reason, the volume of the remnant liver is one of the major limiting factors in hepatic surgery. A future liver remnant (FLR) that is 20% of the original organ is considered a safe parameter after extensive resection in cases where the liver is healthy and does not show any pathologic changes, ie, signs of steatosis or fibrosis.[7] Frequently, patients with multiple liver lesions need to

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Abbreviations and Acronyms

ALPPS = associating liver partition and portal vein ligation for staged hepatectomy
CRM = colorectal metastasis
CTx = chemotherapy
FLR = future liver remnant
PT = partial thromboplastin time
PVE = portal vein embolization

undergo extended right hepatectomy, which includes segments IV to VIII. This procedure removes about 84% of the liver's volume.[8] A number of functional and imaging procedures have been developed to assess both the size and function of the FLR preoperatively. In cases in which insufficient liver volume is of major concern, FLR strategies like portal vein embolization (PVE) or portal vein ligation have been developed to increase the prospective remnant liver volume as a means of preventing liver failure.[9-11] Recently, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been described as a viable procedure for routine extended liver resection in order to successfully increase the volume of the FLR.[12]

Virtually all patients undergoing hepatic resection for colorectal liver metastasis (CRM) are also subjected to hepatotoxic neoadjuvant chemotherapy (CTx). Drug-specific histologic changes, such as steatohepatitis, sinusoidal obstruction syndrome, and steatosis increase postoperative morbidity and mortality rates.[13] The use of CTx regimens has led to improved oncologic and survival outcomes after resection of CRM, decreasing both the tumor load and the amount of tissue that needs to be resected.[14] Even though agents that reduce CTx-induced hepatic injury have been described,[15] the use of CTx can cause substantial damage to the liver, which ultimately limits the amount of resectable tissue. Because most patients with CRM undergo neoadjuvant CTx, this study was performed to assess its effect on hypertrophy of the FLR during ALPPS. Additionally, because it is known that ALPPS is accompanied by substantial morbidity and mortality, we present the overall 1-year survival in our cohort.

METHODS

Patients and procedures

Nineteen consecutive patients who underwent ALPPS between September 2011 and April 2014 were analyzed. Last follow-up was in September 2014. Data examined included age, sex, liver function parameters, body mass index (BMI), imaging, hospital course (including morbidity and mortality), and outcome. Volumetry was performed before liver partitioning and hepatectomy. Complications are presented according to the definitions of the International Study Group of Liver Surgery (ISGLS) and the Dindo-Clavien classification.[6,16-18] Long-term outcomes of all patients were retrospectively analyzed. Overall survival (OS) was defined from the date of the hepatectomy until death or September 2014. Disease-free survival (DFS) was determined from the hepatectomy until recurrence at any site. Bilirubin and partial thromboplastin time (PT) levels were analyzed a day before surgery, as well as on postoperative days 1 and 3. These parameters were also assessed a day before the second operation, as well as 1, 3, and 10 days after the second surgical procedure (Table 1 and Fig. 1).

Surgical procedure

In all cases, liver partitioning was performed after intraoperative ultrasound was done to evaluate resectability. Hilar structures were exposed, and the right portal vein was closed either by vascular stapler or ligature. Complete hepatic arterial perfusion was preserved. Additionally, all portal, arterial and biliary branches of segment IV were divided while segment I branches could be preserved. Parenchymal transection was performed either by LigaSure (Covidien) or Cavitron Ultrasonic Surgical Aspirator (CUSA, Valleylab) without use of a Pringle maneuver.[19] After partitioning, the liver was wrapped in a protective plastic bag to prevent adhesions (Fig. 2). After approximately 1 week, hypertrophy of the FLR took place and was confirmed with a CT scan before either right or extended right hepatectomy were performed.

In the case of a right hepatectomy, the right hepatic artery and venous drainage of the right and middle hepatic vein into the vena cava were divided and ligated, either by endovascular stapler or ligature. In 38% of the patients,

Table 1. Demographics and Preoperative Liver Function

	Total			Chemotherapy			No chemotherapy			
Variable	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	p Value
Age, y	59.1	11.9	31–78	55.6	10.6	31–66	63.8	11.2	46–78	0.15
Bilirubin, mg/dL	1.3	2.1	0.2–9.3	0.5	0.2	0.2–1	2.5	2.7	0.6–9.3	0.03
Prothrombin time, %	96	24.3	12.1–121.7	98.2	13.5	77.7–125	93	32.7	12.1–121.7	0.35