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ORIGINAL ARTICLE

Importance of primary indication and liver function between stages: results of a multicenter Italian audit of ALPPS 2012–2014

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Abstract

Background: Posthepatectomy liver failure is one of the most feared complications in extended hepatic resections. In 2012, a novel two-stage liver resection was developed, able to induce rapid and extensive hypertrophy by portal vein ligation and in situ liver splitting – Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS). The technique became more widely employed but its use remained controversial due to reporting of high complication and mortality rates.

Method: A national audit was performed to gather information about the safety of the procedure and to better understand the complications. The audit was offered to all high-volume hepatobiliary centers in Italy.

Results: Of all Italian centers approached in January 2012, 12 centers with experience in ALPPS enrolled and participated in collection of data. Fifty patients underwent ALPPS between 2012 and 2014. In 48/50 patients completion of hepatectomy was performed successfully. Major morbidity occurred in 54% with a 20% 90-day mortality. Uni- and multivariate analysis showed that ALPPS for cholangiocarcinoma and a peak of bilirubin over 5 mg/dl between stages was associated with increase of 90-day mortality and worse survival.

Discussion: It is proposed that a moratorium be introduced for classic ALPPS in cholangiocarcinoma and to abort ALPPS in patients who develop an interstage increase in bilirubin, due to the high risk of liver failure and mortality.

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Introduction

When the liver remnant is too small to sustain post-resection liver function, portal vein occlusion techniques such as portal vein embolization (PVE) or portal vein ligation (PVL) are used routinely to increase the future residual liver volume.[1,2] In 2012 a new surgical technique was introduced that combines PVL with in situ splitting of the liver parenchyma, Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS).[3,4] Despite rapid and impressive FLR hypertrophy and several studies demonstrating the potential of ALPPS to extend limitations for resectability, concerns about complications and mortality were brought forward, which led to ongoing controversy about its safety.

Given that ALPPS has exceedingly rare indications and is associated with a mortality that is clearly above 5%, single center series are insufficient to gain knowledge about the safety of ALPPS. An international registry initiated by the University of Zurich, reported a 90-day mortality of 9%, but was based on voluntary reporting and likely underestimates true mortality due to incomplete reporting in about 20% of patients and a potential selective reporting bias due to the voluntary character of the

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See group of Group authors at the end of the article.

registry.[5] Concerns about the safety of ALPPS led us to initiate a collaborative national registry in Italy to gather data prospectively from monitored surgical centers to assess true mortality and its risks.

The primary aim was to assess the safety of ALPPS in the experience of Italian surgeons. The secondary objective was to identify risk factors to provide guidance on how to use this surgical innovation.

Methods

Study design

All high-volume hepatobiliary centers in Italy were approached in January 2012 and offered the opportunity to participate in a national audit of patients treated with an ALPPS procedure. Participating centers committed to include all consecutive patients in their hospital undergoing ALPPS. Others, not reported herein, either refused to send their data or did not perform any ALPPS at the time.

The Italian ALPPS registry was approved by the respective ethical committees of each center. All patients entered into the registry approved inclusion of their data into an anonymized database. Data entry was performed into electronic spreadsheets by the surgeons performing the procedures. Data entered were monitored by the study center in Maggiore Hospital and complete data entry of all ALPPS patients performed in each center was confirmed. In March 2012, data entry commenced at the Department of Surgery at Maggiore Hospital. Following the enrollment of the 50th patient on February 28th 2014, the analysis data set for this study was created and analyzed.

Variables

The main outcomes of this study were 90-day mortality and complications as well as independent predictors of survival after ALPPS by uni- and multivariate analysis. Liver remnant volumes were assessed using cross-sectional imaging by computed tomography (CT) or magnetic resonance imaging (MRI) and standardized future liver remnant (sFLR) was assessed in each patient using the Vauthey formula: $-794.41 + 1267.28 \times$ body surface area (m^2).[6,7] Volumetry was performed using dedicated volume rendering software. In patients with bilobar involvement, FLR was calculated by subtracting the tumor volume (clean FLR).

Liver function tests were documented preoperatively and every other day postoperatively. Preoperative cholestasis was defined, similarly to previous studies, as preoperative bilirubin >2.9 mg/dl.[8] Complications were classified according to the Clavien classification of surgical complications[9] and grade $\geq$ IIIA was considered a "major" complication. Posthepatectomy liver failure (PHLF) was classified according to the ISGLS definition.[10] Data on oncologic staging were entered according to the pathology assessments at each center.

Surgical technique

The ALPPS surgical technique was performed according to its inaugural description.[11] The nomenclature defined in the first report from the International ALPPS registry was used to describe ALPPS resection types.[12] All cases were performed by the same surgeon of each single center.

Study size and bias

Based on literature reports, a mortality of 10% (5 patients) was expected and it was planned that the first analysis of the registry using safety endpoints should be performed after enrollment of 50 patients. Since ALPPS was used for three very different oncological indications and due to the small number of cases, patients were classified into 3 groups for analysis: liver metastases, biliary malignancies and hepatocellular carcinoma.

The biases intrinsic to registry reports with voluntary data entry were prospectively addressed. Since many participating centers were at the beginning of their learning curve for ALPPS, the audit was only offered to high-volume hepatobiliary centers to limit its potential impact when analyzing outcomes.

All consecutive patients at each center were enrolled into the registry to reduce reporting bias (principle of consecutivity). Centers were advised to also enter patients who did not proceed to complete resection in either stage to reduce reporting bias (principle of intent to treat). Entries were confirmed at the time of analysis by a retrospective audit through the study center in Maggiore Hospital (principle of audit). These principles were introduced to address concerns voiced about voluntary registry reports and to allow us to give a valid assessment of the safety of the procedure.

Statistical analysis

Data were expressed in median and range and the Kruskal–Wallis or median test were used for comparisons. Fisher's Exact test was used for comparisons of categorical variables. Univariate logistic regression analysis was applied in order to investigate risk factors for mortality and major complications. Survival analysis was performed with using a Cox Proportional Hazard Model. Variables found different in the univariate analysis with an α-value of 0.10 or which were clinically significant according to our judgement were included in a multivariate model and then excluded through a backward elimination procedure with $\alpha \leq 0.05$. Receiver operating characteristic (ROC) curve analysis was performed to identify the cut-off value of peak bilirubin between stages in predicting 90-day mortality. The cut-off value was determined by seeking the largest sum of the sensitivity and specificity values, while maintaining the lowest likelihood ratio of a negative test and the highest likelihood ratio of a positive test. All analyses were performed using the statistical software R (Foundation for Statistical Computing, Vienna, Austria).