Thirty-day mortality leads to underestimation of postoperative death after liver resection: A novel method to define the acute postoperative period

Tobias S. Schiergens, MD,[a] Maximilian Dörsch, MD,[a] Laura Mittermeier, MSc,[b] Katharina Brand, MSc,[b] Helmut Küchenhoff, PhD,[b] Serene M. L. Lee, PhD,[a] Hao Feng, MD,[a] Karl-Walter Jauch, MD,[a] Jens Werner, MD,[a] *and* **Wolfgang E. Thasler, MD,[a]** *Munich, Germany*

Background. *Postoperative mortality commonly is defined as death occurring within 30 days of surgery or during hospitalization. After resection for liver malignancies, this definition may result in underreporting, because mortality caused by postoperative complications can be delayed as the result of improved critical care. The aim of this study was to estimate statistically the acute postoperative period (APP) after partial hepatectomy and to compare mortality within this phase to standard timestamps.*
Methods. *From a prospective database, 784 patients undergoing resection for primary and secondary hepatic malignancies between 2003 and 2013 were reviewed. For estimation of APP, a novel statistical method applying tests for a constant postoperative hazard was implemented. Multivariable mortality analysis was performed.*
Results. *The APP was determined to last for 80 postoperative days (95% confidence interval 40–100 days). Within this period, 55 patients died (7.0%; 80-day mortality). In comparison, 30-day mortality (N = 32, 4.0%) and in-hospital death (N = 39, 5.0%) were relevantly less. No patient died between postoperative days 80 and 90. The causes of mortality within 30 days and from days 30–80 did not greatly differ, especially regarding posthepatectomy liver failure (44% vs 39%,* P *= .787). Septic complications, however, tended to cause late deaths more frequently (43% vs 25%,* P *= .255). Comorbidities (Charlson comorbidity index ≥3;* P *= .046), increased preoperative alanine aminotransferase activity (*P *= .030), and major liver resection (*P *= .035) were independent risk factors of 80-day mortality.*
Conclusion. *After liver resection for primary and secondary malignancies, 90-day rather than 30-day or in-hospital mortality should be used to avoid underreporting of deaths. (Surgery 2015;158:1530-7.)*

From the Department of General, Visceral, Transplantation, Vascular and Thoracic Surgery,[a] Hospital of the University of Munich; and Department of Statistics,[b] Ludwig-Maximilians-University, Munich, Germany

An increasing number of patients are considered for operative treatment of malignant liver lesions because resection remains the best and only potentially curative therapeutic option. As diagnostic and operative techniques as well as perioperative care have markedly improved during the last several decades, the rate of resections will continue to increase.[1,2] Furthermore, criteria for surgery have been expanded greatly towards a more aggressive approach, especially for liver metastases.[2,3] As a consequence, it is crucial to consider perioperative mortality when obtaining informed consent and evaluating individual risks and benefits of liver surgery. In this context, operative mortality traditionally has been reported as death within 30 days after surgery or during hospitalization[1,3-15]; however, 30-day, 90-day, and in-house-mortality rates used to indicate early procedural outcome after liver resection have been published nonuniformly, which hinders the interpretation and comparison of mortality rates and risk factors. Careful patient selection on the basis of outcome

Accepted for publication July 4, 2015.

Reprint requests: Wolfgang E. Thasler, MD, Professor of Surgery, Department of General, Visceral, Transplantation, Vascular and Thoracic Surgery, Hospital of the University of Munich, Marchioninistr. 15, D-81377 Munich, Germany. E-mail: wolfgang.thasler@med.lmu.de.

0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2015.07.019

predictors is the key for decreasing postoperative death.[13] On the basis of individual observations, some studies have found that 90-day mortality rates after liver resection[16] or other major abdominal surgery[4] are clearly greater than 30-day mortality rates, which may be attributable to improvements in critical care that delay death to beyond 30 days after surgery.[4] Furthermore, deaths related to liver resection also can occur after hospital discharge. These findings indicate the necessity of defining precisely the acute postoperative period (APP) in this patient population so that mortality rate and risk factors of mortality are reported in a proper and standardized manner. A scientific assessment of the duration of the APP based on precise statistical analysis, however, has not yet been performed.

Thus, the aim of the present study was to define precisely the APP after resection of primary and secondary malignant liver tumors by applying novel statistical analyses. This study also compared the mortality rate observed during the statistically determined APP to the 30-day and in-hospital mortality rates.

PATIENTS AND METHODS

Design, study population, and data assessment. Data of patients undergoing elective liver resection with curative intent between 2003 and 2013 were collected prospectively. This study was approved by the Ethics Committee, Faculty of Medicine, Ludwig-Maximilians-University. The study design, data acquisition, statistical methods, and manuscript preparation were carried out following the STROBE guidelines.[17] For prospective standardized data assessment, electronic case report forms were used as reported previously.[18] Comorbidities were stratified using the classification of the American Association of Anesthesiologists as well as the Charlson comorbidity index.[19] The type of liver resection was classified using the Brisbane nomenclature.[20] Steatosis, fibrosis, and cirrhosis were assessed systematically by gross and microscopic pathology. Steatosis was defined as the presence of at least 5% steatotic hepatocytes.[21] Major resection was defined as hemihepatectomy or extended hemihepatectomy. Postoperative complications were assessed according to the validated Clavien-Dindo classification.[22] Posthepatectomy liver failure (PHLF) was defined according to the definition by the International Study Group of Liver Surgery.[23] Thirty-day and in-hospital mortalities as well as death within the statistically calculated APP were assessed.

Statistical analysis. The R-language (version 3.1.0, Vienna 2014) and SPSS (version 22.0; IBM, Armonk, NY) were used for the statistical analysis. Binominal variables are expressed as numbers and percentages, and continuous variables are expressed as medians and ranges [minimum and maximum] or means ± standard deviation. For comparison, the χ^2 test or Fisher exact test (expected frequency <5) was used depending on the character of the variable. In addition, to compare risk factors associated with mortality occurring within the APP in our population to those identified in populations of previously published studies, univariable and multivariable regression was performed. For multivariable analysis, variables were entered into a hierarchical stepwise logistic regression analysis.

For estimation of the APP, the transition point t between the acute and postacute postoperative phase was statistically assessed. From the postoperative daily hazard rate of the entire study population which indicates the probability to die on the next day (the Figure), the day t after surgery was identified, beyond which the hazard rate became constant (transition or change point). Thus, t indicated the beginning of the postacute phase. For this purpose, we used a method for change point estimation based on data of threshold estimation published by Mallik et al.[24] The hazard rate h_1 was assumed to be constant beyond one year after surgery and was estimated based on the overall survival data of the study population. Subsequently, a series of tests for the hazard rate being equal to h_1 at intervals of 20 days was conducted. This was performed by a binomial test using the number of persons at risk and the number of surviving patients. This resulted in a series of P values for intervals from 20 to 40 days to 340–360 days. Prior to the change point (acute phase), significantly greater hazards for the intervals are assumed (small corresponding P-values), whereas after t (postacute phase), no significance for intervals would be assumed (high corresponding P-values). Thereby, the transition point t could be estimated from this series of P-values. The 95% confidence interval (95% CI) was calculated using the nonparametric bootstrap method. The method's performance was validated within a parallel statistical simulation study (data not shown).

RESULTS

Patient population. Between 2003 and 2013, 1,032 patients underwent resection of benign and malignant liver tumors. None of the patients with benign tumors ($N = 95$) died within 90 days after surgery, and this population was excluded from the analysis. After further exclusion of 153 patients because of incomplete case report forms,