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Liver Transplantation for Metastatic Neuroendocrine Tumors: Outcomes and Prognostic Variables

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Abstract

Background: Patient selection for liver transplantation for metastatic neuroendocrine tumors remains a topic of debate. There is no established MELD exception, making it difficult to obtain donor organs.

Methods: A multicenter database was created assessing outcomes for liver and multivisceral transplantation for metastatic neuroendocrine tumors and identifying prognostic factors for survival. Demographic, transplant, primary tumor site and management, pathology, recurrent disease and survival data were collected and analyzed. Survival probabilities were calculated using the Kaplan–Meier method.

Results: Analysis included 85 patients who underwent liver transplantation November 1988–January 2012 at 28 centers. One, three, and five-year patient survival rates were 83%, 60%, and 52%, respectively; 40 of 85 patients died, with 20 of 40 deaths due to recurrent disease. In univariate analyses, the following were predictors of poor prognosis: large vessel invasion (P<0.001), extent of extrahepatic resection at liver transplant (P=0.007), and tumor differentiation

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(*P*=0.003). In multivariable analysis, predictors of poor overall survival included large vessel invasion (*P*=0.001), and extent of extrahepatic resection at liver transplant (*P*=0.015).

Conclusion: In the absence of poor prognostic factors, metastatic neuroendocrine tumor is an acceptable indication for liver transplantation. Identification of favorable prognostic factors should allow assignment of a MELD exception similar to hepatocellular carcinoma.

Keywords

liver transplantation; neuroendocrine tumor; prognostic indicators

INTRODUCTION

Gastroenteropancreatic neuroendocrine tumors (NET) arise from neuroendocrine cells present throughout the body. They are generally classified as islet cell or carcinoid and can occur in various anatomic sites resulting in a variety of presentations, with 32–47% of patients found to have metastatic disease at the time of diagnosis [1]. The incidence, recently reported at 5.25 per 100,000, has been rising in recent years, and the prevalence is 35 per 100,000 [1,2].

Slow-growing NETs have often metastasized to the liver by the time of diagnosis and negatively impact survival [3–5]. Various medical and surgical therapeutic options exist for metastatic NET to the liver, and the appropriate therapy remains a topic of discussion [6–11]. Liver resection has been shown to improve survival in selected cases [12–16]. Ki-67 index, tumor differentiation, and tumor stage have been identified as prognostic factors for patients who are candidates for resection [4,17,18]. International groups have incorporated these factors into proposed guidelines for the selection of patients for surgical resection [5,8,19]. In cases in which resection is not possible, total hepatectomy and liver transplantation (LT) have been performed for alleviation of tumor burden, symptom control, potential for cure, and for complications from prior therapy. Early reports were limited to single centers with few cases making it difficult to develop specific guidelines for transplant candidacy. Recently, there have been efforts to combine large numbers of cases from multiple centers as well as for single centers to develop and evaluate strategies to better define the utility of LT for metastatic NET.

Increasing interest has focused upon how to apply collective experience of LT for metastatic NET to establish evidence-based selection criteria. Two prospective studies have each achieved high survival outcomes of 78.3% and 87% through the use of strict selection criteria [20,21]. There have been several single center retrospective studies [20–25] as well as several meta-analyses and transplant registry-based studies [26–29] addressing this topic. Combining multicenter data has resulted in the ability to analyze outcomes and prognostic factors in larger populations. The largest and most recent multicentric report involved an analysis of the risk factors and outcomes for 213 patients from 35 European centers who underwent transplant from November 1982 through December 2009 and revealed several negative prognostic factors including hepatomegaly, poor differentiation, and major resection at the time of transplant [30]. When the United Network for Organ Sharing (UNOS) data was analyzed the only factor to achieve statistical significance was waiting

time: 5-year overall survival with a waiting time longer than the median (67 days) was 63% versus 36% for patients who waited less than 67 days [26]. However, these results were based upon the limited information in the UNOS system. To date, no large multicenter North American experience including the preoperative and pathologic variables has been published to corroborate and expand upon the European experience.

Our aim was to develop a database of patients who had undergone LT for metastatic NET to identify demographic, histologic, site, and management-specific prognostic factors for overall survival. Secondary endpoints included graft survival as well as disease recurrence and causes of death.

MATERIALS AND METHODS

The patient population was initially identified by querying UNOS regarding centers and dates in which LT was performed for metastatic NET since 1988. After initial contact, we were notified by several centers that there were additional cases, and a request for participation in data collection was extended to both U.S. and Canadian centers. In addition, an attempt to collect global data led to one European center contributing data. Collected data included: demographics, type of transplant (multivisceral versus liver alone), type of donor (live donor versus deceased donor), patient and graft outcomes, disease status at last follow up, and cause of death and/or graft loss. Disease-specific data included location, histology, and management of primary site and medical and surgical therapies for primary site and metastatic disease. All transplant pathology reports were collected and reviewed by an independent pathologist to collect histologic data including cell type, differentiation, lymphatic, and vascular invasion, number of nodules, and tumor burden. Operative and pathology reports were used to corroborate center-supplied data, confirm the diagnosis, and obtain additional information for the database. Disease recurrence at last visit was recorded, however specific data regarding the timing and site of recurrence was rarely provided due to the retrospective nature of the study. Cause of death and cause of graft loss was reported by each center.

In order to assess the effect of timing of resection of primary site as well as extrahepatic surgeries at the time of transplant, the type of surgery was categorized as follows: Type 1=multivisceral transplantation; Type 2=pancreaticoduodenectomy at the time of LT; Type 3=distal pancreatectomy with splenectomy and bowel resection at LT; Type 4=distal pancreatectomy with or without splenectomy at LT; Type 5=bowel resection at LT; Type 6=no additional extrahepatic surgery at LT. The University of Southern California Institutional Review Board approved this study.

Statistical Methods

The primary endpoint considered in the analysis was patient survival. Survival was defined as the duration in time between date of transplant and date of death with patients who were alive censored at the last follow-up date. Besides patient survival, graft survival, which was defined as the duration in time between date of transplant and date of graft loss at retransplant or death, was also analyzed. Death was considered an event in the analysis of graft survival, and patients who were alive without experiencing a retransplant were

censored at the last follow-up date. Date of retransplant was unknown for one patient; in the calculation of graft survival, the shortest graft survival duration (which was less than one day) was assigned to that patient.

Survival probabilities were calculated using Kaplan–Meier method with Greenwood standard errors. Univariable and multivariable Cox regression analyses were performed to evaluate the association between patient/disease characteristics and patient survival and to estimate hazard ratios. All *P*-values reported were two-sided, and a *P*-value of ≤ 0.05 was considered statistically significant. All analyses were performed in STATA (version 11.0; StataCorp LP College Station, TX).

RESULTS

29 centers (27U.S, one Canadian and one European) contributed 94 cases. All pathology reports were reviewed and only those cases in which NET was confirmed were included in the analysis, resulting in a total of 28 centers contributing 85 patients who underwent LT between November 23, 1988, and January 1, 2012. These included 34 females and 51 males, with median age at transplant of 48 years (range 16–75 years) and median follow up of 2.7 years (range 0.05–21.4 years). Patient and tumor characteristics, location and management of primary site, transplant type, and decade of LT are described in Table I. LT alone was performed in 80% of patients with the remaining 20% undergoing multivisceral transplant. There were 42 pancreaticoduodenal primaries (including ampulla and pylorus), and 24 primaries in the digestive tract. One patient had a primary lung tumor, one had both pancreatic and bowel tumors, one had a choledochal cyst, and the primary site was never identified in 16 patients. Table II shows the timing of resection according to anatomic site.

As of the last follow-up date, 40 patients (47.1%) have died. Recurrent disease was the cause of death in 20 patients, whereas 18 patients died of causes unrelated to NET and two patients died of unknown causes. Disease status was reported in 81 patients, and a total of 46 of these 81 patients were found to have recurrent disease during the follow-up period.

One, three, and five-year patient survival was 83%, 60%, and 52% (Fig. 1). One, three, and five-year graft survival was 79%, 56%, and 43%.

Univariate analysis results are shown in Table III. Large vessel invasion ($P < 0.001$, Fig. 2a) and differentiation ($P=0.003$, Fig. 2b) correlated with patient survival. Although it did not achieve statistical significance, five-year patient survival was 76% for patients without lymph node invasion compared to 49% for those with lymph node invasion ($P=0.063$, Fig. 2c). Transplant decade after year 2000 ($P=0.074$) trended toward but did not reach statistical significance. When primary site of the tumor was considered, five-year patient survival was 53% for duodenum/pancreas compared to 51% for digestive tract ($P=0.84$, Fig. 3). Age greater than or equal to 50 approached statistical significance in the subset of patients undergoing liver transplant alone after the year 2000 ($P=0.057$).

While one-year patient survival rates were similar for LT alone and for multivisceral transplant, five-year survival was lower for multivisceral transplant (40%) than for LT alone (55%; $P=0.11$). Patient survival according to timing of resection did not achieve statistical

significance although five-year survival was higher in patients who had the primary tumor removed before transplant (58%, *P*=0.19, Fig. 4a). The extent of resection required for the primary tumor at the time of transplant correlated significantly with five-year survival, with patients undergoing multivisceral transplant or requiring combined pancreatic and bowel resection (Types 1–3) demonstrating significantly lower survival than those who either had no concomitant surgery or underwent an isolated pancreatic or bowel resection (Types 4–6) (*P*=0.007, Fig. 4b).

We included lymph node invasion, large vessel invasion, and extent of resection in a multivariable Cox regression model to evaluate their joint association with patient survival. For lymph node invasion and large vessel invasion, patients were grouped into three groups (no, yes, unknown); for extent of resection, we utilized the grading system defined above. In this multivariable analysis, large vessel invasion (yes vs. no; *P*=0.001) and extent of resection (*P*=0.015) were both found to be significantly associated with patient survival. The difference between the presence or absence of lymph node invasion was not significant (P=0.24). Differentiation was not included due to the small sample size for which these data are available. To examine whether large vessel invasion and extent of resection could be combined into a scoring system to identify patients more likely to survive post LT, we counted the number of adverse features each patient had. Therefore a score of 0 corresponded to no large vessel invasion and an extent of surgery type 4, 5, or 6. In addition, large vessel invasion was unknown for 38 patients, and those patients were scored 0 for large vessel invasion. A score of 1 point corresponded to large vessel invasion or extent of surgery type 1, 2, or 3 (but not both). A score of 2 points corresponded to larger vessel invasion and extent of surgery type 1, 2, or 3. One, three and five-year patient survivals were 90%, 79%, and 66% for score 0, 84%, 37%, and 37% for score 1, and 52%, 17%, and no follow up for score 2 (Fig. 5). This was statistically significant with a *P*-value of <0.001. When this analysis was redone excluding the 38 patients with unknown large vessel invasion, the conclusions did not change.

DISCUSSION

The overall survival in our patient population is similar to that reported in other large studies. Despite high recurrence rates, the five-year survival is 52%. While this does not compare favorably with survival in the modern era, it is necessary to view this survival rate in the context of the study time period, which began in 1988. In an analysis of outcomes using UNOS data, Gedaly reports 49% five-year survival for LT for metastatic NET compared to 62% for LT for hepatocellular carcinoma [26]. LeTreut reports the European experience including a five-year survival of 52%, which is identical to our own outcomes [30]. Based on our data and the data of other studies, LT remains indicated for metastatic NET in selected cases.

Central to the discussion of the merit of this procedure is the ability to identify consistent prognostic factors. In this study, univariate analysis identified differentiation, large vessel invasion, and extent of concomitant surgery as significant risk factors for survival. Multivariable analysis confirmed large vessel invasion and extent of surgery as significant factors that held up in a scoring system. We further showed that in this clinical setting, there

is the potential for developing an effective scoring system for identifying patients who are unlikely to benefit from LT. Decade of transplant, type of transplant, lymph node invasion and age greater than 50 in the subset of patients who underwent LT alone after the year 2000 trended towards significance.

A number of literature reviews, registry-based analyses, single-center analyses, and more recently larger multicenter analyses have established that survival outcomes are good enough to merit LT in the setting of NET which has metastasized to the liver. Discussion now centers upon the appropriate determination and use of predictors of prognosis to guide in the selection of patients.

Reviews and Registry Data

Lehnert reviewed the literature encompassing 103 cases. He reported 5-year survival of 47% and multivariable analysis identified adverse prognostic factors as age greater than 50 years ($P<0.03$) and transplantation combined with upper abdominal exenteration or pancreaticoduodenectomy ($P<0.001$) [27].

Gedaly's analysis of LT performed for metastatic NET from the UNOS database from 1988–2008 reported a 5-year survival of 49%, and the only variable to achieve statistical significant improved 5-year survival was waiting time over 67 days [26]. Nguyen reported data from UNOS for the time period 1988–2011 [29]. The 5-year survivals in the post-MELD era for HCC, metastatic NET and non-malignant diseases were 65.4%, 57.8%, and 73.7%. There was no statistical difference for the two malignancies but the survival for non-malignant diseases was significantly better ($P=0.002$). These studies, while providing useful information, reflect the limited data in the UNOS database and do not allow for an analysis of the clinical, pathologic, anatomic, and surgical prognostic factors.

Mathe analyzed 89 cases of NET with a pancreaticoduodenal primary site from 20 studies in the literature and reported five-year survival of 44% [28]. Negative prognostic factors included age greater than or equal to 55 years ($P=0.0242$) and simultaneous pancreatic resection at the time of LT ($P=0.0132$). With 0, 1, or 2 of these prognostic factors, 5-year survival was 61%, 40%, and 0%, respectively ($P=0.0023$). Our data confirm the negative prognosis accompanying pancreatic resection at the time of transplant (we showed that distal pancreatectomy did not worsen prognosis unless combined with bowel resection) but again failed to definitively confirm the age factor.

Single Center Studies

Frilling reported 67.2% five-year survival in 15 patients and identified the following positive prognostic factors: Ki67 index <10%, no extrahepatic disease, and the presence of somatostatin receptors on tumor surface [20]. Van Vilsteren reported 87% one-year survival in 17 patients who underwent transplantation after instituting a protocol using the following criteria: complete excision of primary site >6 months prior to LT, exclusion of poorly differentiated tumors and rectal carcinoid primaries [21]. Additional single center studies with small sample sizes reported 5-year survival ranging from 33–90% and/or cited prognostic factors including simultaneous resections and tumor differentiation [22–24,31–43].

Multicenter Studies

LeTreut reported 47% 5-year patient survival in 85 patients from 17 centers in France [44]. On univariate analysis, poor prognostic variables included hepatomegaly, gastrin secretion, upper abdominal exenteration, pancreaticoduodenal primary, positive resection margins, and poor differentiation. Resection of the primary tumor and serotonin secretion were good prognostic variables. On multivariable analysis, primary tumor site in the duodenum or pancreas (P=0.0018), upper abdominal exenteration at surgery (P=0.0034) and hepatomegaly (P=0.0157) were poor prognostic factors. LeTreut also reported an analysis of the risk factors and outcomes for 213 patients from 35 European centers who underwent transplant from November 1982 through December 2009 [30]. Five-year patient survival was 52% [30]. Multivariable analysis revealed the following negative risk factors: major resection at time of transplant (P<0.0001), poor differentiation (P<0.0005), and hepatomegaly (P<0.0003). Five-year survival improved to 59% for the subset of 106 patients who underwent LT after 2000. A separate multivariable analysis on these 106 patients revealed the following risk factors: hepatomegaly (P=0.006), age greater than 45 years (P=0.073) and resection in addition to LT (P=0.058). Utilizing a point system in which one point was given for each of these three prognostic factors, 5-year patient survival was 77%, 79%, 39%, and 33% for 0, 1, 2, and 3 points, respectively.

Our study did not confirm age to be a significant risk factor, however, there was a trend for age to have an impact in the modern era as it did in the European experience. Overall simultaneous resection did not reach significance, but extent of simultaneous resection was significant in our study confirming an impact of extrahepatic resection at the time of LT on outcomes. In addition, our study identified large vessel invasion as a significant prognostic factor.

Combining our data with prior reports, it is clear that certain factors repeatedly stand out as impacting patient survival. Tumor differentiation and extent of simultaneous surgery have been adequately validated. Other factors including age greater than 45–55 depending upon the study and the era, hepatomegaly, large vessel invasion, timing of primary site resection, and transplant era have been shown to be significant in various studies and have trended towards significance in others. The role of age, management of primary site and the role of preoperative imaging to evaluate vascular involvement all warrant further consideration. Hepatomegaly would represent tumor burden and a further look at this issue is required as it is usually the issue preventing other successful modalities such as resection.

The limitations of this study included the inability to determine disease-free survival and the small number of pathology reports stating tumor differentiation and Ki67 status. Although the data demonstrated that long-term survival can be expected even in the face of recurrence, the lack of data pertaining to time, location, and management of disease recurrence made an analysis of disease free survival and prognostic factors for disease recurrence impossible.

There was a lack of uniformity inherent in a retrospective study, as well as the time span covered, in the pathology reports. Overall assessment of the cell type, presence, and extent of vascular or lymphatic invasion, tumor burden and differentiation were not uniformly reported. Differentiation was specifically reported in less than half of the cases with very

few reports specifically reporting Ki67. Currently proposed WHO (2010) pathological classification of neuroendocrine tumors (NET), considers the Ki-67 proliferation index as the main criterium for the grading of NET. Continued progress in this field would be facilitated by consistent reporting policies that include the reporting of both positive as well as negative findings.

In recent years targeted medical therapies have been approved in the treatment of NET. Sunitinib, a receptor tyrosine kinase inhibitor, has been shown to prolong progression-free survival over placebo in patients with advanced pancreatic neuroendocrine tumors [45,46]. Everolimus, a mammalian target of rapamycin inhibitor, has also shown increase of progression-free survival over placebo [46]. Everolimus is approved for the prophylaxis of rejection in liver transplant recipients and its role in patients undergoing liver transplant for metastatic NET needs to be determined. The potential exists that with the development of new agents and the implementation of multidisciplinary protocols, the outcomes may be improved.

CONCLUSION

The recent expansion of literature in this field has clarified the role of LT in metastatic NET confirming a role for LT in this disease process. The identification of significant risk factors has allowed us to better select our patients and consideration should be given to the development of a scoring system to allow for MELD exceptions to allow improved access to organs for well-selected patients.[47]

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Abbreviations:

LT	liver transplantation
NET	neuroendocrine tumor
UNOS	United Network for Organ Sharing

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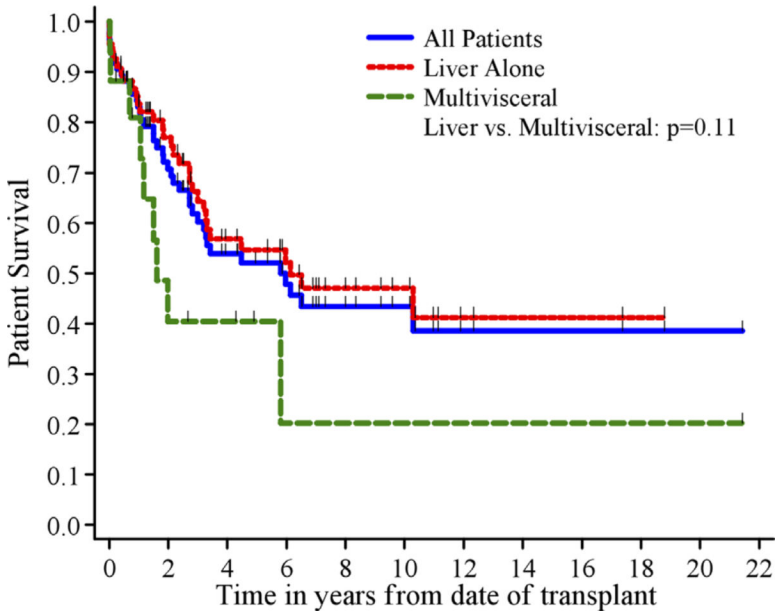

Fig. 1.
Patient survival by transplant type.

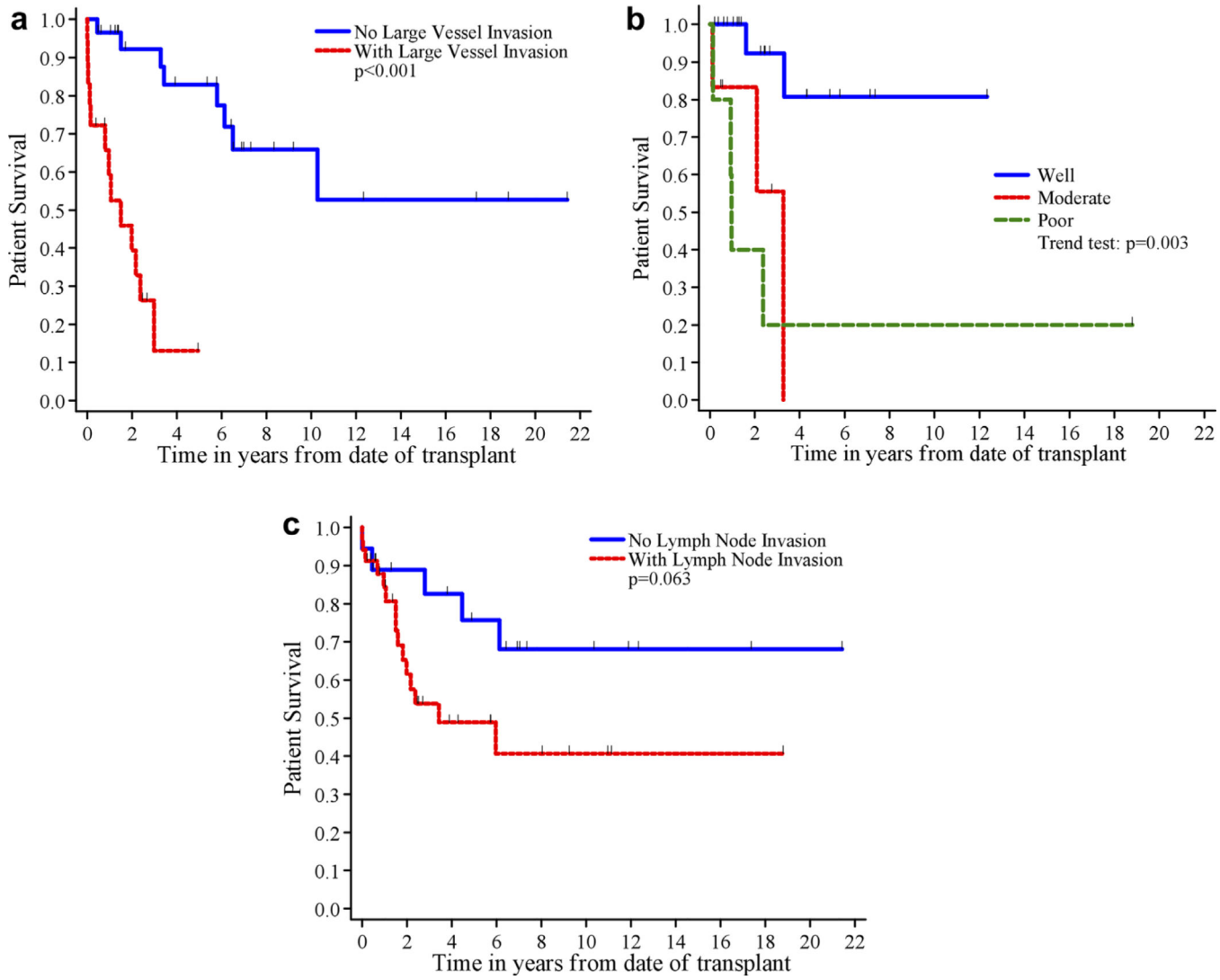

Fig. 2.

a: Patient survival by large vessel invasion. b: Patient survival by differentiation c: Patient survival by lymph node invasion.

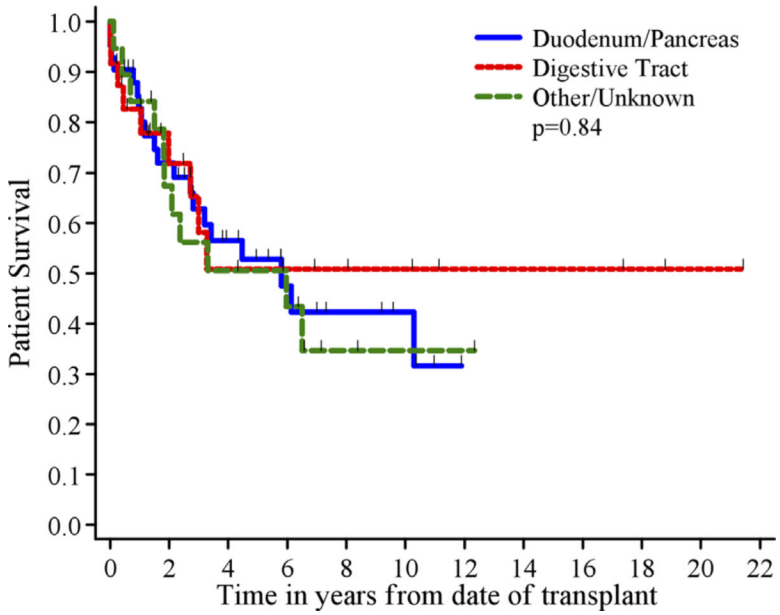

Fig. 3.
Patient survival by primary site of tumor.

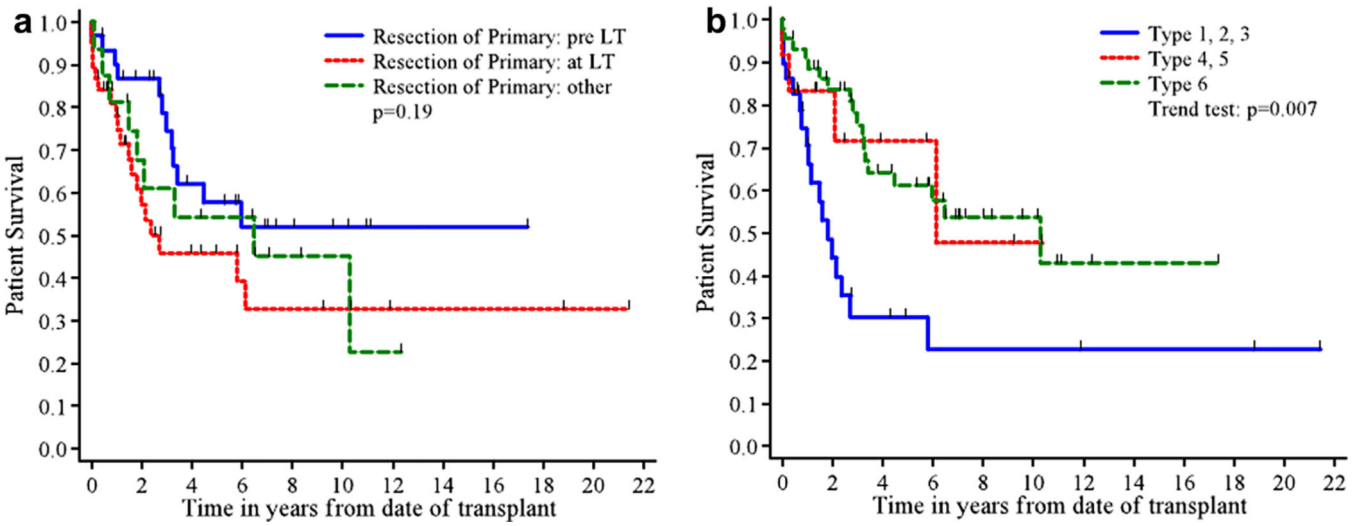

Fig. 4.

a: Patient survival by timing of resection. b: Patient survival by extent of resection.

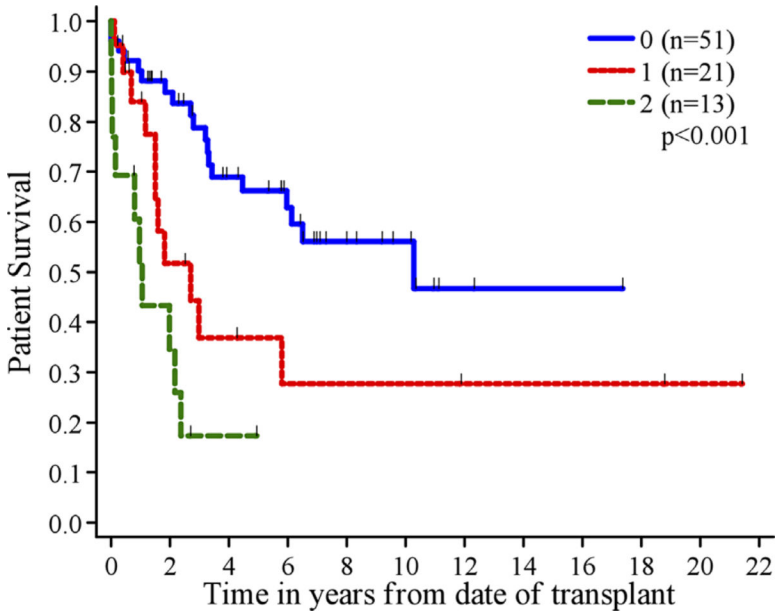

Fig. 5.
Patient survival by scoring system.

TABLE I.

Patient and Disease Characteristics

Variables	Total (N=85)	%
Age at transplant		
< 50 years	46	54.1
≥ 50 years	39	45.9
Gender		
Female	34	40.0
Male	51	60.0
Transplant Type		
Liver Alone	68	80.0
Multivisceral	17	20.0
Primary Site of the Tumor		
Duodenum/Pancreas	42	49.4
Digestive Tract	24	28.2
Other/Unknown[a]	19	22.4
Cell Type		
Carcinoid	35	41.2
Islet Cell	34	40.0
Unknown	16	18.8
Timing of primary tumor resection		
Pre- transplant	31	36.5
At time of transplant[b]	38	44.7
Other[c]	16	18.8
Lymph node invasion		
No	18	21.2
Yes	34	40.0
Unknown	33	38.8
Large vessel invasion		
No	29	34.1
Yes	18	21.2
Unknown	38	44.7
Decade of transplant		
Before 2000	29	34.1
In or After 2000	56	65.9
Extent of extrahepatic resection at transplant[d]		
Type 1	17	20.0
Type 2	9	10.6
Type 3	3	3.5
Type 4	5	5.9
Type 5	7	8.2

Variables	Total (N=85)	%
Type 6	44	51.8
Differentiation		
Well	21	24.7
Moderate	6	7.1
Poor	5	5.9
Unknown	53	62.4

[a]"Other/Unknown" included lung (n=1), choledochal cyst (n=1), pancreas and small bowel (n=1), and unknown (n=16).

[b]This category included six patients whose primary tumor resection was performed pre-transplant and additional extrahepatic tumor resection was performed at transplant.

[c]"Other" included patients who never had resection (n=15) or whose resection was done after transplant (n=1).

[d]"Type 1= multivisceral transplant, Type 2=pancreaticoduodenectomy, Type 3=distal pancreatectomy, splenectomy and bowel resection, Type 4=distal pancreatectomy±splenectomy, Type 5=bowel resection, Type 6=no additional surgery at transplant.

TABLE II.

Timing of Resection According to Anatomic Site

Site	Resection Pre-transplant	Resection at transplant	Resection Pre- and at transplant	Resection Post-Transplant	No resection
Pancreas (n = 38)	12	22[a]	3	1	0
Small bowel (n = 16)	8	5[a]	3	0	0
Duodenum (n = 2)	1	1	0	0	0
Ampulla (n = 1)	1	0	0	0	0
Choledochal cyst (n = 1)	0	1	0	0	0
Pylorus (n = 1)	0	1	0	0	0
Gastric (n = 4)	3	1[a]	0	0	0
Large bowel (n = 1)	1	0	0	0	0
Appendix (n = 1)	1	0	0	0	0
Rectum (n = 2)	2	0	0	0	0
Lung (n = 1)	1	0	0	0	0
Pancreas and small bowel (n= 1)	1	0	0	0	0
Unknown (n=16)	0	1[a]	0	0	15

[a]12 of 22 pancreatic primaries, 3 small bowel, 1 gastric primary and 1 unknown primary underwent multivisceral transplant.

TABLE III.

Patient Survival (PS) and Hazard Ratios (HR) for Patient Subsets (N=85)

Variables	n	# Events	1 year PS±SE (%)	3 year PS±SE (%)	5 year PS±SE (%)	HR (95%CI)	*P*
Age at transplant							
<50 years	46	19	78±6%	65±7%	59±8%	1.0	0.32
>50 years	39	21	90 ±5%	54±9%	44±9%	1.4 (0.73, 2.5)	
Gender							
Female	34	17	82 ±7%	54±9%	51 ±9%	1.0	0.63
Male	51	23	84 ±5%	64±7%	53±8%	0.86 (0.46, 1.6)	
Transplant type							
Liver alone	68	31	84 ± 5%	64 ± 6%	55 ± 7%	1.0	0.11
Multivisceral	17	9	81 ± 10%	40 ± 14%	40 ± 14%	1.9 (0.90, 4.0)	
Primary site of the tumor							
Duodenum/pancreas	42	20	83±6%	63±8%	53 ± 9%	1.0	0.84
Digestive track	24	9	83±8%	58 ±12%	51 ±12%	0.85 (0.38, 1.9)	
Other/unknown[a]	19	11	84 ±8%	56 ±12%	51 ±12%	1.1 (0.53, 2.3)	
Timing of primary tumor res.							
Pre-transplant	31	12	90 ±5%	75±8%	58 ±10%	1.0	0.19
At time of transplant[b]	38	19	78±7%	46±9%	46±9%	1.9 (0.94, 4.0)	
Other[c]	16	9	81±10%	61±13%	54 ±13%	1.5 (0.63, 3.6)	
Lymph node invasion							
No	18	5	89±7%	83±9%	76 ±11%	1.0	0.063
Yes	34	15	84 ±6%	54 ±10%	49±10%	2.5 (0.90, 7.0)	
Unknown	33	20	79±7%	55±9%	43±9%		
Large vessel invasion							
No	29	8	97±3%	92 ±5%	83±8%	1.0	<0.001
Yes	18	13	59±12%	13 ±11%	13±11%[d]	12 (3.7, 42)	
Unknown	38	19	84 ±6%	57±9%	46±9%		
Decade of transplant							
Before 2000	29	21	76 ±8%	55±9%	41±9%	1.0	0.074

Variables	n	# Events	1 year PS±SE (%)	3 year PS±SE (%)	5 year PS±SE (%)	HR (95%CI)	*P*
In or after 2000	56	19	87±5%	63±7%	60±8%	0.56 (0.30, 1.1)	
Extent of resection							
Type 1	17	9	81±10%	40±14%	40±14%	0.81 (0.70, 0.94)[f]	0.007
Type 2	9	7	67±16%	13 ±12%	13 ±12%		
Type 3	3	2	33±27%	33±27%	33±27%		
Type 4	5	1	100%	100%	100%		
Type 5	7	3	71±17%	48±23%	48 ±23%		
Type 6	44	18	91 ±4%	75±7%	61±8%		
Differentiation							
Well	21	2	100%	92±7%	81 ±13%	3.1 (1.5, 6.6)[g]	0.003
Moderate	6	3	83±15%	56±25%	56±25%[e]		
Poor	5	4	40 ±22%	20 ±18%	20 ±18%		
Unknown	53	31	81 ±5%	56±7%	50±7%		

SE: Standard Error; HR: Hazard Ratio; CI: Confidence Interval

[a] "Other/Unknown" included lung (n=1), choledochal cyst (n=1), pancreas and small bowel (n=1), and unknown (n=16).

[b] This category included 6 patients whose primary tumor resection was performed pre-transplant and additional extrahepatic tumor resection was performed at transplant.

[c] "Other" included patients who never had resection (n=15) or whose resection was done after transplant (n=1).

[d] No follow-up was available at 5 years. PS at 4 years was reported.

[e] No follow-up was available at 5 years. PS at 3 years was reported.

[f] Extent of resection was evaluated as a continuous variable in the Cox regression models. The HR represents each unit change in grading of extent of resection.

[g] Differentiation was evaluated as a continuous variable in the Cox regression models. The HR represents each unit change in grading of extent of resection. "Unknown" was excluded from the Cox models.