



Long-term outcome of liver transplantation for unresectable liver metastases for Neuroendocrine neoplasms: a Belgian retrospective multi-center study

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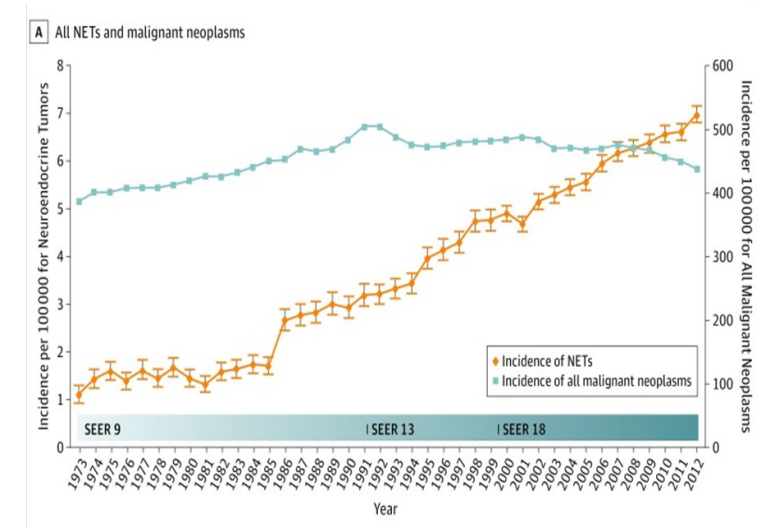
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Neuroendocrine Neoplasms - NEN

- Rare neoplasms that arise from cells of the neuroendocrine system
 - Incidence in 2012 6/100.000 habitants/year
 - Prevalence around 35/100.000 habitants
- Heterogenous biologic behavior
- Variable clinical presentation:
 - from incidental diagnostic to extensive metastatic disease
- When metastases occur, more than 50% are liver metastases



Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States.
 A. Dasari et al *JAMA Oncol.* 2017;3(10):1335-1342.

NEN Liver Metastases Treatment

- Resection of liver metastases is the most effective option
- Curative liver metastases resections show good overall survival at 5 years
 - DFS varies from 29% to 96%
- However in 80% of patients, NEN liver metastases are nonresectable
- For select patients with nonresectable NEN liver metastases, liver transplantation is the only curative treatment currently available
 - Milan criteria
 - Low grade tumor
 - Portal vein drainage
 - Metastatic diffusion of less than 50% of liver parenchyma
 - Disease stability for at least 6 months before liver transplantation

Single Center Belgium experience on Liver transplantation for unresectable liver mets for NEN

Liver transplantation and neuroendocrine tumors: lessons from a single centre experience and from the literature review

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Table 3. Neuroendocrine tumor (NET) and liver transplantation: outcome of UCL-series and selection policy.

Patient	OLT	LT-year	Disease free survival (%)					Patient survival (%)				
			Months	Mean ± SD (months)	1 year	3 years	5 years	Months	Mean ± SD (months)	1 year	3 years	5 years
1	84	1987	10.9	17.4 ± 7.4	75	0	0	51.5	59.3 ± 43.1	10	75	25
2	167	1988	25.3					46.2				
3	229	1988	12.2					17.0				
4	263	1989	22.0					119				
5*	1094	2000	4.8	34.6 ± 29.2	80	40	20	11.4	67.9 ± 33.2	80	80	60
6	1195	2001	12.2					68.4				
7	1224/1395	2002	42.0					96				
8	1290	2002	35.2					84				
9	1311	2003	78.9					78.9				
Total				26.9 ± 23	77	22	0		64.1 ± 35.5	88	77	33

*LT, despite thoracic primary tumor, due to huge tumor bulk.

- Patient survival
- Patients transplanted before 1990
 - 5-year survival: 25%
- Patients transplanted after 1999
 - 5-year survival: 60%
- No NEM liver transplants in the 1990s

Single center Belgium experience updated on Liver transplantation for unresectable liver mets for NEN

Original Article/Transplantation

Secondary non-resectable liver tumors: A single-center living-donor and deceased-donor liver transplantation case series

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Table 3

Characteristics of primary tumors (neuroendocrine tumor)

LT No.	Year of LT	Primary tumor location	G	T	N	M	Pre-LT primary tumor surgery	Pre-LT CT	Pre-LT somatostatin analogues	Pre-LT antibiotics	Pre-LT LRT	Carcinoid syndrome
Living donor liver transplantation - neuroendocrine tumor liver metastases												
1290	2003	Small bowel	1	3	2	0	Small bowel resection	No	Yes	No	No	Yes
1695	2009	Pancreas	2	3	1	1	Distal spleno-pancreatectomy	No	No	No	Yes ^a	No
							Left colectomy					
							Left adrenalectomy					
							Liver metastasectomy (twice)					
1721	2009	Small bowel	2	X ^b	X	1	Small bowel resection after LT	No	Yes	No	Yes ^c	Yes
1732	2009	Pancreas	3	2	1	1	Duodeno-pancreatectomy	No	No	Yes	No	No
							Liver metastasectomy					
2028	2013	Small bowel	1	4	1	1	Small bowel resection	No	Yes	No	No	No
2197	2016	Pancreas	2	2	1	1	Pancreatectomy with enucleation (main lesion)	EVL	No	No	No	Yes
							Partial duodenectomy (second lesion)					
2200	2016	Pancreas	2	4	0	0	Distal spleno-pancreatectomy	No	No	Yes	No	No
							Left colectomy					
2225	2016	Small bowel	1	1	1	1	Small bowel resection	No	No	No	Yes ^d	No
2246	2016	Pancreas	2	3	0	1	Duodeno-pancreatectomy	No	Yes	No	No	Yes
							Liver metastasectomy					
Deceased donor liver transplantation - neuroendocrine tumor liver metastases												
84	1987	Pancreas	2	X ^b	X	1	Distal spleno-pancreatectomy after LT	No	No	No	No	No
229	1988	Pancreas	3	2	0	1	Distal spleno-pancreatectomy	No	No	No	Yes ^e	No
							Liver metastasectomy					
263	1989	Pancreas	2	2	NA	1	Spleno-pancreatectomy (MEN1)	No	No	No	No	Yes
1195	2001	Small bowel	1	1	0	1	Small bowel resection	No	No	No	No	No
1224	2002	Pancreas	3	X ^b	X	1	Duodeno-pancreatectomy after LT	EVL	No	No	No	No
							Deogastric surgery		Yes	No	No	No
1511	2003	Possibly gastric	1	X ^b	X	1	Distal spleno-pancreatectomy	No	No	Yes	Yes ^d	No
1942	2012	Pancreas	2	3	1	1	No	No	No	Yes	No	No
2005	2013	Biliary tract	1	2	1	1	No	No	Yes	No	No	Yes
2261	2016	Pancreas	1	2	1	1	Duodeno-pancreatectomy	No	Yes	Yes	No	No
							Liver metastasectomy					

CT: cholangitis; CT: chemotherapy; DDK: diazoxide; ETP: etoposide; EVL: enucleation; G: differentiation grade of neuroendocrine tumors (good = 1, moderate = 2, poor = 3) following ENETS classification [11]; LRT: loco-regional treatment; LT: liver transplantation; MEN1: multiple endocrine neoplasia type 1; NA: not available.

^a Liver transplant chemotherapy.

^b Primary tumor not found before liver transplantation.

^c Liver metastasectomy ablation.

^d Primary tumor never found.

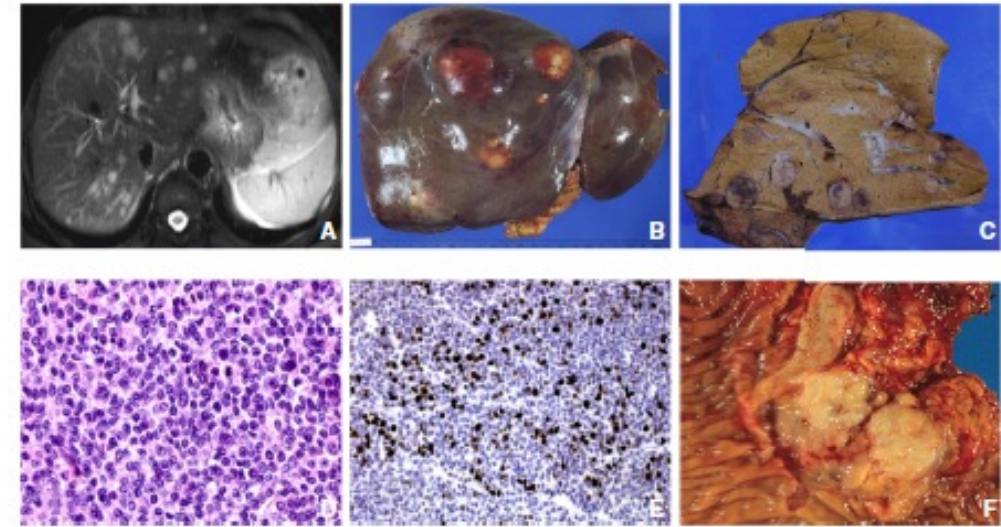


Fig. 1. Case No. 1224: a 39-year old female patient undergoing deceased-donor liver transplantation for neuroendocrine liver metastases. A: CT scan showing multiple, bi-lobar (biopsy proven) metastases; B and C: The pathological examination of the hepatectomy specimen revealed innumerable lesions; D and E: HE staining shows a high mitotic index and immunohistochemistry shows a Ki67 expression of 35% (original magnification x 100); F: Seven months after LT, a poorly differentiated (G3) primary tumor was found in the pancreatic head and a pylorus preserving pancreatoduodenectomy was performed. This patient is alive and disease-free 225 months after diagnosis and 210 months after transplantation.

- 18 patients transplanted for Net Liver Metastases
- 9 using a deceased donor liver graft (4 deaths)
- 9 using a living donor liver graft (all currently alive)

Secondary non-resectable liver tumors: A single-center living-donor and deceased liver transplantation case series. J. Lerut et al. *HPDI* 18 (2019), 412-422.

Aim of the study

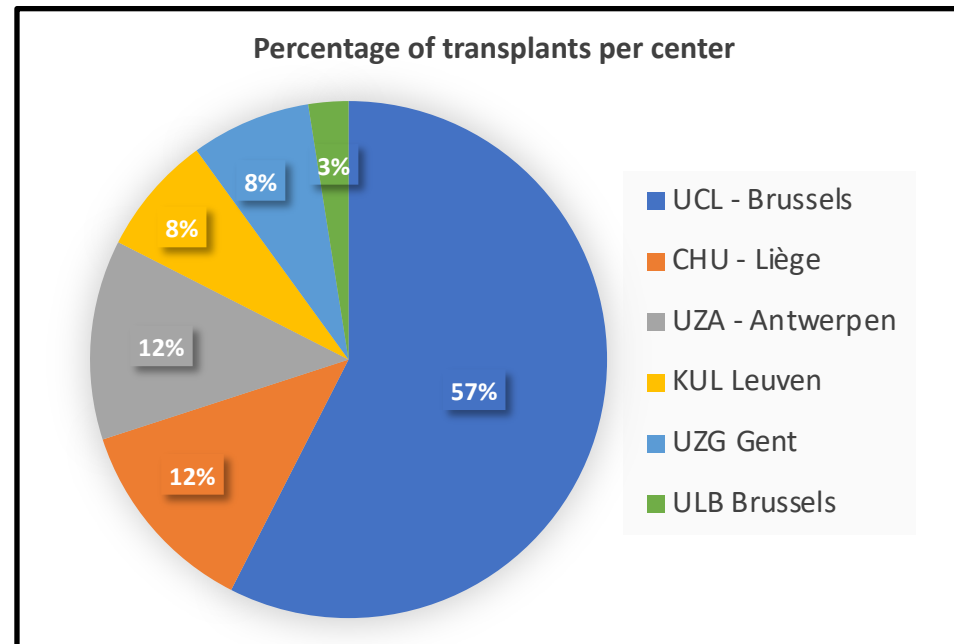
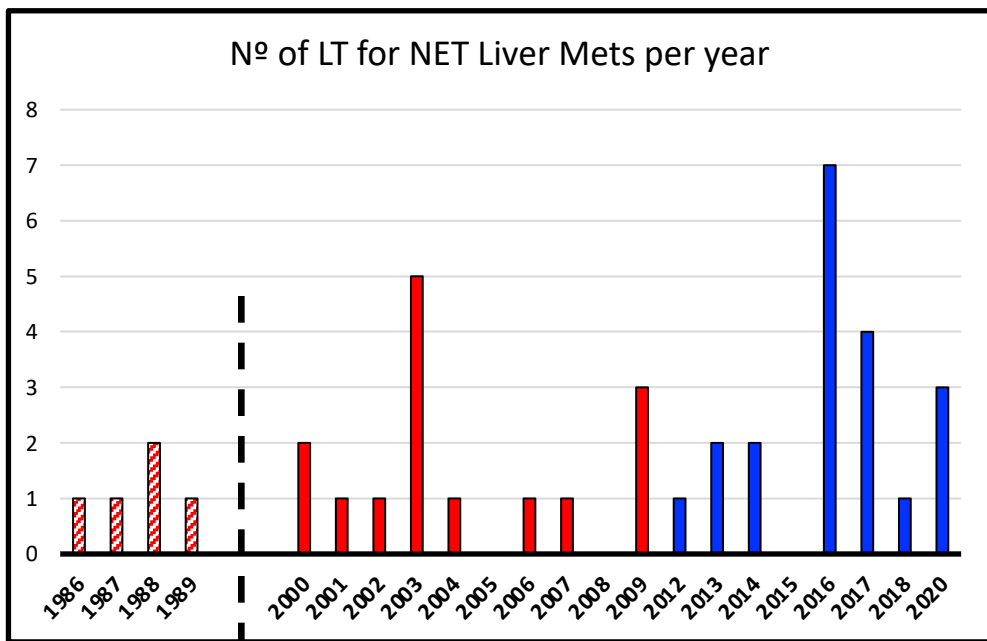
- Describe the Multicenter Belgium experience for patients transplanted for NEN liver metastases over time
 - Evaluate the patient survival and disease free survival
 - Evaluate patterns of NET recurrence after Liver Transplantation
 - Describe possible factors contributing to recurrence

Material and Methods

- Multi-center study
 - All 6 liver transplant centers in Belgium
- CUSL – UCL - Ethical committee approval
- BeLIAC endorsement → posterior approval by local ECs in each transplant center
- Retrospective data collection from January 1986 to December 2020
 - Electronic patient data and hard copy data

Results – Patient Population

- 40 patients transplanted for NEN liver metastases from 1986 to 2020
 - 75 % males
 - Young population
 - Mean age at TU diagnostic (years): 41.9 ± 10.9 Median: 43.5 (19 – 61)
 - Mean age at Liver Transplantation: 47.1 ± 11.5 Median: 46.5 (23 – 69)
 - Delay between tumor diagnostic and treatment: 7.5 months



Primary Tumor Characteristics

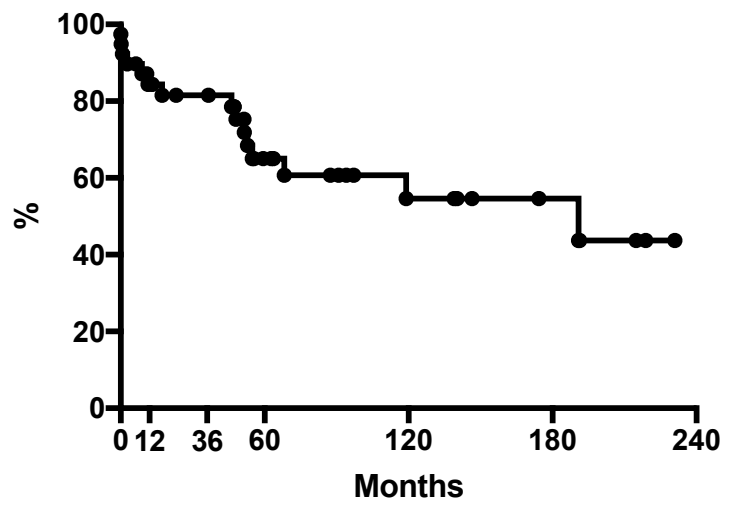
	Total Population 40 (100%)	Transplanted before 2010 20 (50%)	Transplanted after 2010 20 (50%)	<i>p</i>
Primary tumor site				
Pancreas	23 (57%)	11 (55%)	12 (60%)	NS
Small bowel	10 (25%)	5 (25%)	5 (25%)	NS
Duodenum	1 (2.5%)	1 (5%)	0	NS
Stomach	2 (5%)	0	2 (10%)	NS
Biliary tree	1 (2.5%)	0	1 (5%)	NS
Unknown	1 (2.5%)	1 (5%)	0	NS
Bronchial tree	2 (5%)	2 (10%)	0	NS
Histologic grade WHO				0.02
Grade 1	10 (25%)	5	5	
Grade 2	17 (42.5%)	6	11	
Grade 3	5 (12.5%)	2	3	
Not defined	8 (20%)	8	0	
Endocrine Syndrome	16 (40%)	7 (44%)	9 (56%)	NS
Primary tumor resection prior LT	34 (85%)	17 (50%)	17 (50%)	NS

Liver Metastases Characteristics

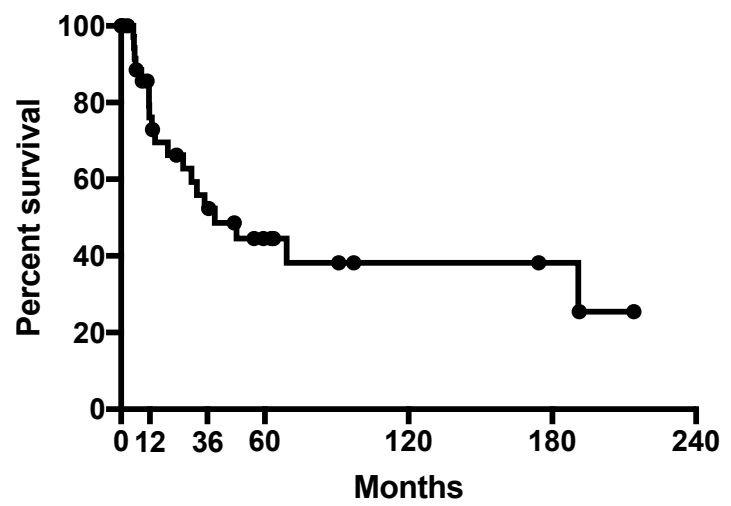
	Total Poulation 40 (100%)	Transplanted before 2010 20 (50%)	Transplanted after 2010 20 (50%)	<i>p</i>
Synchronic liver metastases	25 (64%)	14	11	NS
Liver Metastases treatment prior LT (data available for 34 pts)	34	17	17	
Surgical resection	10 (29.4%)	5 (29.4%)	5 (29.4%)	NS
Somatostatin analogues	18 (53%)	8 (47.1%)	10 (58,8%)	NS
Sunitinib	9 (26.5%)	2 (11.8%)	7 (41,2%)	0.052
Everolimus	5 (14,7%)	0	5 (29,4%)	0.015
Locoregional treatment	13 (38,5%)	5 (29,4%)	8 (47,1%)	NS
Chemotherapy	8 (23,5%)	6 (35,3%)	2 (11,8%)	NS
IFN	3 (8,8%)	3 (17,6%)	0	0.07
Time between tumor diagnosis and LT (months)	49.53 (5.6 - 152.7)	40.2 (5.6 – 126)	63 (24 – 152.7)	NS

Results – Survival rates

Patient Overall Survival

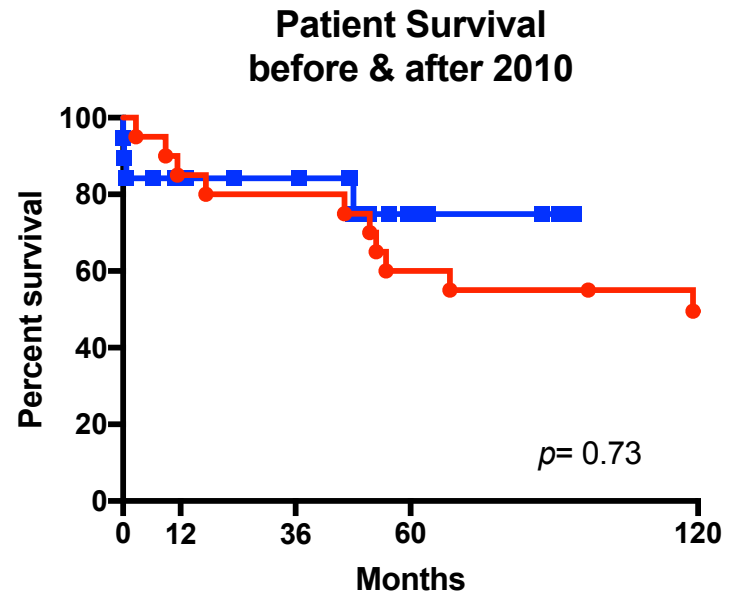


Overall Disease Free Survival

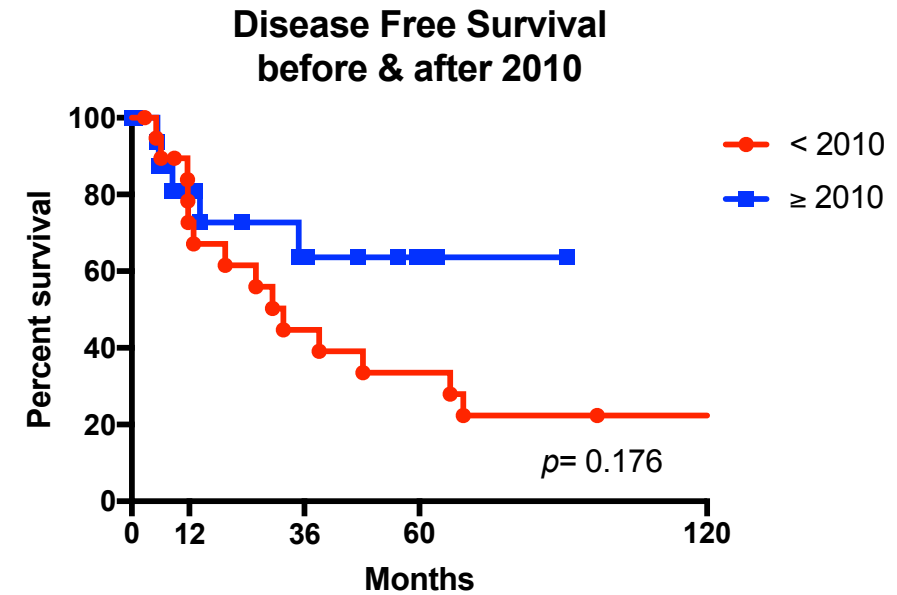


	Overall Survival	Disease Free Survival
1-year	84.3%	76.3%
3-year	81.6%	52.3%
5-year	65%	44.5%
10-year	54.6%	38.2%

Survival rates according to different periods of time

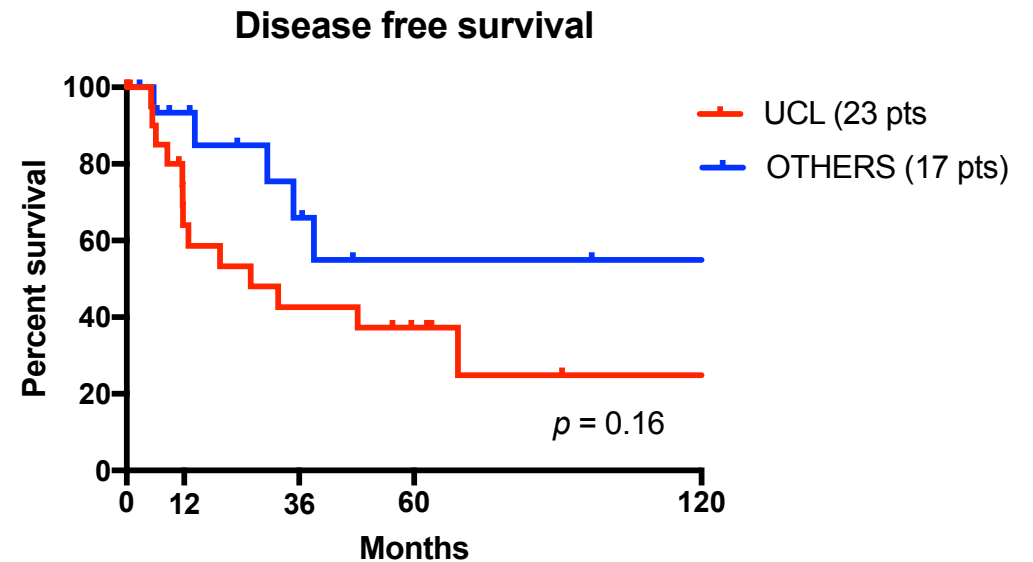
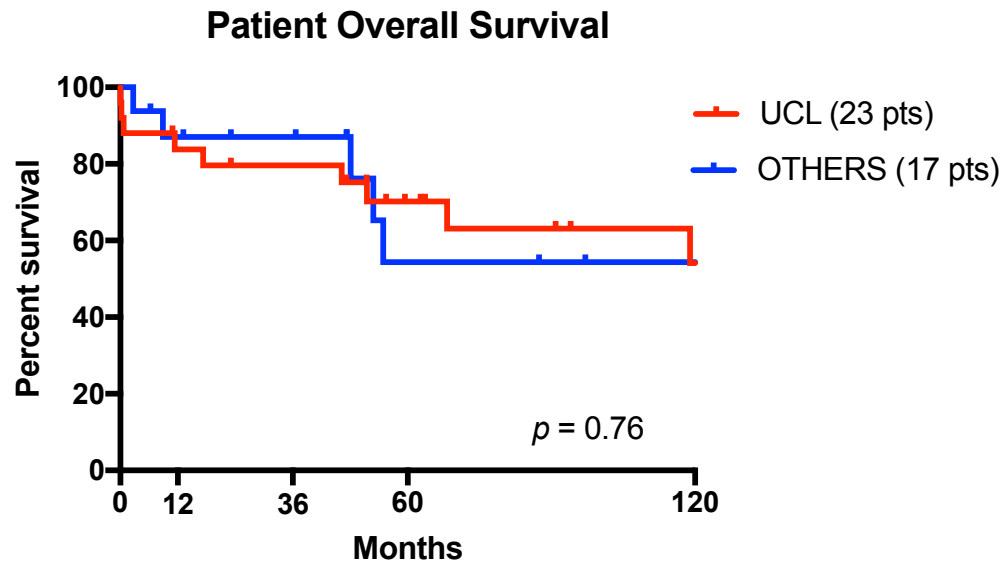


Patient survival	Transplanted < 2010	Transplanted > 2010
1-year	85.0%	84.2%
5-year	60.0%	74.8%
10-year	49.5%	74.8%



Disease Free Survival	Transplanted before 2010	Transplanted after 2010
1-year	72.7%	80.8%
5-year	33.6%	63.6%
10-year	22.4%	63.6%

Survival rates according to transplant center volume

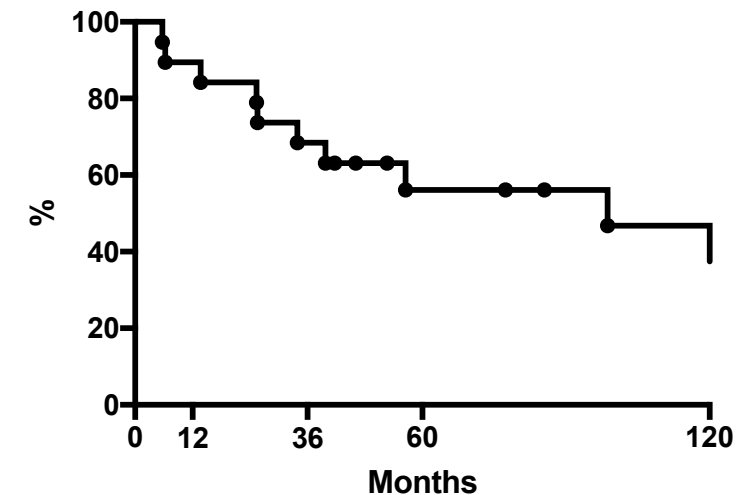


Post LT NEN recurrence

	Total Poulation	Transplanted before 2010	Transplanted after 2010	<i>p</i>
Patients with recurrence	19 (47.5%)	14 (73.7%)	5 (26,3%)	0.011
Site of recurrence				
Lymph nodes	12	8 (66,7%)	4 (33,3%)	NS
Liver	8	7 (87,5%)	1 (12,5%)	0,027
Lungs	5	3 (60%)	3 (40%)	NS
Pancreas	4	4 (100%)	0	0,045
Bones	8	6 (75%)	2 (25%)	NS
Skin	1	1 (100%)	0	NS
Diaphragm	2	2 (100%)	0	NS
Peritoneum	1	1 (50%)	1 (50%)	NS
Pelvis	1	1 (100%)	0	NS
Kidneys	1	1 (100%)	0	NS
Small bowel	1	1 (100%)	0	NS
Spleen	1	1 (100%)	0	NS

Recurrence treatment	Patients
Surgical resection	8
Re-transplantation	2
Somatostatin analogues	6
Chemotherapy	6
Sirolimus	2
Sunitinib	4
Radiotherapy	2

Patient survival after recurrence



Conclusions

- Liver transplantation for NEN nonresectable liver metastases presented good short and long-term results in our series
- Long-term survival rate is not influenced by the number of transplants per center
 - Selective liver transplantation indication criteria (after 2007)
- Better overall survival and disease free survival rates for patients transplanted after 2010
- Recurrence is very frequent (around 50% of transplanted patients)
 - Improvement of the disease free survival after 2010
- However good survival rate after recurrence
 - Recurrence treatment has probably contributed to these findings

Thank for your attention

