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Review

Controversies in defining prognostic relevant selection criteria that determine long-term effectiveness of liver resection for noncolorectal nonneuroendocrine liver metastasis

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HIGHLIGHTS

- Refinements in surgical technique have improved the safety of liver resection.
- Surgery for noncolorectal nonneuroendocrine liver metastasis is controversial.
- Factors that determine survival outcome after surgery are not jet defined.
- The group of patients who would benefit from surgery is still unknown.
- Further research is needed to identify effective predictors of outcome.

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ABSTRACT

The usefulness of liver resection in the treatment of colorectal liver metastasis and metastases from neuroendocrine tumors of the gastrointestinal tract has been studied extensively. However, the role and utility of surgery in treating patients with noncolorectal nonneuroendocrine liver metastasis (NCNNLM) is poorly defined and controversial. Despite the broadening indications of liver resection for NCNNLM, the group of patients who would benefit from surgery is still unknown. Because tumor biologies among NCNNLM vary widely, it has been difficult to determine which factors influence overall survival. Attempts have been taken in the literature to identify a variety of factors which may influence outcome following liver resection for NCNNLM. Almost all of these data are drawn from retrospective studies, and its relevance to contemporary practice is not known. Many centers have published prognostic factors which influence survival; jet the results are contradictory for these factors. There is no uniformity in the various prognostic factors reported. This review has been undertaken to provide an overview of these important controversies.

1. Introduction

Liver resection is commonly performed for treatment of colorectal liver metastases (CRLM) and metastases from neuroendocrine tumors of the gastrointestinal tract (GIT). Depending on selection criteria of patients with CRLM for liver resection, 5-year survival rates up to 58% have been reported [1,2]. The outcome of liver resection is even better for metastases from neuroendocrine tumors of the GIT with reported 5-year survival rates as high as 76% [3]. While the surgical treatment of CRLM and metastases from neuroendocrine tumors of the GIT has been studied extensively, the treatment of noncolorectal nonneuroendocrine liver metastases (NCNNLM) has not. Particularly the role and utility of surgery in treating patients with NCNNLM is poorly defined and controversial. This discrepancy may be due to the fact that liver metastases from other cancers typically occur in the setting of widespread systemic failure, whereas tumors arising within the portal system possess a greater proclivity for establishing truly isolated hepatic metastases [4,5].

There are a sizable number of published studies reporting the results of surgical treatment of NCNNLM (Tables 1 and 2). These data on liver resection for patients with NCNNLM are partly encouraging. Refinements in surgical technique, together with improved understanding of hepatic anatomy, have significantly improved the safety of liver resection. Thus, even the most extensive hepatic resection can now be performed with an operative mortality of less than 5% [5,6] if the liver to be resected is without chronic damage. Based on this technical improvement, liver resection for NCNNLM has gained acceptance over the past decades and the indications

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Table 1
Overview of major publications describing patients undergoing liver resection for noncolorectal nonneuroendocrine liver metastases.

Author	Year period	Year published	Follow-up, mo	DFI, mo	n	np	Synchronous, %	Metachronous, %	5-year OS, %
Harrison [6]	1980–1995	1997	20	36	96	17	23	77	37
Elias [12]	1984–1996	1998	nr	nr	112	12	nr	nr	18–46
Lang [9]	1983–1993	1999	nr	nr	140	20	32	68	24
Hemming [25]	1978–1998	2000	22	12	37	14	38	62	45
Laurent [42]	1980–1997	2001	22	27	39	15	15	85	35
Yamada [43]	1990–1995	2001	nr	nr	33	9	56	44	12
Ruth [44]□	1991–1999	2001	44	nr	27	13	25	75	35
Karavias [45]	1994–2000	2002	38	nr	18	6	56	44	nr
Ercolani [15]	1990–2003	2005	36	12	83	15	13	87	34
Weitz [22]	1981–2002	2005	26	41	141	23	28	72	17
Yedibela [14]□	1978–2001	2005	nr	25	162	9	44	56	26
Cordera [23]	1988–1998	2005	nr	12	64	17	31	69	30
Adam [21]	1983–2004	2006	31	38	1452	18	24	76	36
Earle [20]	1990–2005	2006	nr	22	69	12	22	78	31
Lendoire [17]	1989–2006	2007	28	29	106	14	23	77	19
Reddy [24]	1995–2005	2007	59	85	82	17	26	74	37
O'Rourke [18]	1986–2006	2008	20	42	102	22	27	73	39
Lehner [16]	1994–2008	2009	nr	50	242	19	19	81	28
Groeschl [5]	1990–2009	2012	30	43	420	6	26	74	31

Year period, the time period when the liver resections were done; follow-up indicates median follow-up in months; DFI (Disease-free interval), time interval between the treatment of primary tumor and diagnosis of metachronous liver metastases in months; n, total number of investigated patients; np, the minimum number of types of tumors included in the study; OS, overall survival; □, include also patients with liver metastases of neuroendocrine primary tumors; nr, not reported.

Table 2
Outcome after liver resection.

Author	n	Morbidity, %	Mortality %	R0, %	r, %	lr, %	dr, %	ldr
Harrison [6]	96	nr	0	nr	nr	nr	nr	nr
Elias [12]	112	nr	2	75	nr	nr	nr	nr
Lang [9]	140	33	6	66	nr	nr	nr	nr
Hemming [25]	37	nr	0	100	nr	nr	nr	nr
Laurent [42]	39	8	0	nr	59	31	18	10
Yamada [43]	33	21	9	76	nr	nr	nr	nr
Ruth [44]□	27	23	0	85	67	11	37	19
Karavias [45]	18	11	0	nr	33	17	16	nr
Ercolani [15]	142	21	0	59	45	nr	nr	nr
Weitz [22]	141	33	0	82	66	nr	nr	nr
Yedibela [14]□	162	29	4	62	nr	nr	nr	nr
Cordera [23]	64	7	2	88	66	35	53	48
Adam [21]	1452	22	2	83	67	24	18	25
Earle [20]	69	16	2	88	nr	nr	nr	nr
Lendoire [17]	106	nr	2	90	nr	nr	nr	nr
Reddy [24]	82	30	4	79	57	32	68	nr
O'Rourke [18]	102	21	1	83	70	nr	nr	nr
Lehner [16]	242	21	2	87	nr	nr	nr	nr
Groeschl [5]	420	20	2	87	66	39	50	23

R0, curative resection; r, recurrence; lr, local regional recurrence; dr, distant recurrence; ldr, both local and distant recurrence; nr, not reported; □, include also patients with liver metastases of neuroendocrine primary tumors.

for liver resection have widened considerably. However, the effectiveness and oncological benefit of such surgery remains unclear, which could partly be due to lack of consistency in defining factors that determine survival outcome after surgery. The encouraging results in the literature are mostly achieved in highly selected patients. Thus, there is still no definite conclusion how much the liver resection itself is contributing to the outcome and how much is from the favorable biology of selected patients who might have done well regardless. It is conceivable that the encouraging results were more a reflection of extreme selection bias than the surgical procedure itself. In general, patient selection criteria depend primarily on the biology of the primary tumor. On the other side, because tumor biologies among NCNNLM vary widely (6–23 different entities in the reviewed studies), it has been difficult to determine which factors influence overall survival. Thus, the proper selection of patients that may benefit from liver resection is difficult and remains the most critical issue. Therefore, several controversial issues remain to be studied including the significance of the type of primary tumor, the prognostic value of resection margin, the role of the size of metastatic deposit in the liver and others. Many single center studies attempt to resolve this issue without arriving at a consensus.

The aim of this review was to analyze the ongoing controversies on the impact of pathological variables on outcomes in patients after liver resection for NCNNLM by drawing on clinical data provided in the medical literature.

2. Type of primary tumor

Contrary to CRLM and liver metastases from neuroendocrine tumors where the importance of tumor type on prognosis is clearly documented by the success of surgical removal of the metastatic lesion [3,7,8], data on prognostic implications of the type of the primary tumor after liver resection for NCNNLM are limited.