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Surgical results of liver metastases of tumors other than colorectal-neuroendocrine: Is it really worth it or is it necessary?

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ABSTRACT

Objective: It is known that surgical treatment is advantageous in terms of efficacy and survival in colorectal cancer and neuroendocrine tumor liver metastases. Our aim in this study was to determine the results of surgical treatment of non-colorectal (NCR), non-neuroendocrine tumor (NNET) liver metastases (LM).

Material and Methods: A total of 125 patients having NCR and NNET were included in the study. Demographic characteristics of the patients, histological features of the tumor, time from resection of the primary tumor to the first diagnosis of liver metastases, synchronous and metachronous presentations of hepatic metastases with primary malignancy, type of resection, postoperative complications, length of hospital stay, and survival were analyzed retrosepctively.

Results: Median follow-up time was 21 (1-132) months. Mean overall survival (OS) and mean proression free survival (PFS) were 29.86 ± 2.4 and 21.23 ± 2.1 months respectively. Most of the cases were LM of breast (n= 33, 26.4%), gastric (n= 25, 20.0%) and gastrointestinal stromal tumors (GIST) (n= 16, 12.8%). Interval from resection of primary tumor to the diagnosis of LM was 20.90 ± 28.9 (0-144) months. OS and DFS rates were found respectively as; 78% and 69% at one year, 45% and 38% at three years, 32% and 21% at five years and 3.2% and 1.6% at 10 years. Breast cancer liver metastases had the longest OS and PFS. Pancreatic cancer and gastric cancer group significantly have shorter OS than the other groups.

Conclusion: According to our data, the results are better in breast and GIST liver metastases, and the place of surgical treatment in pancreatic and malignant melanoma liver metastases is controversial.

Keywords: Liver metastases, non-colorectal, non-neuroendocrine

INTRODUCTION

It is well documented that surgical treatment of colorectal cancer liver metastases (CRC-LM), either resection or metastasectomy, has remarkable survival advantages. Therefore, almost all cases of CRC-LM may be candidates for liver surgery regardless of bi-lobar involvement or number and size of nodules (1). Recently, disease free and actual survival rates of CRC-LM get longer with staged hepatectomy, associated liver partition with portal vein ligation for staged hepatectomy (ALPPS procedure) and current chemotherapy modalities (2). Similarly, it has been reported that the surgical treatment of neuroendocrine tumor liver metastases (NET-LM) has been observed to be obviously beneficial on survival rates (3). In addition, liver transplantation can be considered as a treatment modality in NET-LM without extrahepatic disease (4). Considering the aforementioned surgical success, surgery has been preferred as a treatment modality in non-colorectal non -neuroendocrine tumor liver metastases (NCRNNET-LM) in recent years. Analyses of surgical results and survival rates of NCRNNET-LM are not clear due to the limited number of case series which have been reported until now. A few reports including beneficial results have been published (5). However, there are controversies in the recent data about the survival advantages of surgical treatment of some of the NCRNNET-LM including genitourinary, breast and some gastrointestinal tumors other than CRC-LM (6). In addition, a couple of case series including liver metastasectomy for solitary metastases due to very aggressive gastrointestinal tumors like pancreatic cancer have been published (7).

The aim, within the scope of this study, was to evaluate the surgical results and to investigate the effect on survival of NCRNNET-LM, except for CRC and NETs, whose surgical outcomes and survival effects are more clearly known.

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MATERIAL and METHODS

A total of 125 consecutive patients who underwent liver resection (major liver resection, metastasectomy, segmentectomy) because of NCRNNET-LM at a tertiary university hospital between 2003 and 2022 were identified, and the data were obtained from patient records retrospectively. An informed consent form was obtained from all patients. Patients were required to have at least one year of follow-up. Since there were no established resection criteria for the selection of the NCRNNET-LM, patients were evaluated in patient-by-patient manner by a team of oncologists, surgeons and radiologists. Patients having extra hepatic disease and other co-morbidities were excluded. Patients with direct hepatic invasion by extra hepatic primary tumor, cholangiocarcinoma and gall-bladder carcinoma even metachronous cases were also excluded. Negative surgical margins were required in all patients. Patients with positive surgical margins were also excluded from the study. Extrahepatic disease was detected by ultrasonography, computed tomography, magnetic resonance imaging and positron emission tomography. Routine biopsy was not performed in the preoperative period in patients with radiological evaluation of LM. Patients evaluated as having metastatic tumor from the pathology specimens were included in the study.

The demographic features of patients, tumor characteristics and stages, interval from resection of primary tumor to the initial diagnosis of LM, synchronous versus metachronous presentation of hepatic metastases with primary malignancy, type of resections (metastasectomy, segmentectomy or lobectomy), postoperative courses, preoperative and postoperative chemotherapy regimens, the treatment modalities applied in case of recurrence [re-resection and interventional radiological procedures such as trans arterial chemoembolization (TACE), radiofrequency ablation (RFA) and microwave ablation] and long term outcomes were recorded. For breast cancer LM, receptor status (estrogen, progesterone and HER2) were also evaluated. Surgical factors including resection type, simultaneous resection of primary tumor, other concomitant major extra hepatic procedures and resection margin status (microscopically negative R0, or positive R1 resections) were investigated. Major hepatectomy refers to resection of >2 segments, segmental resection refers to resection of 1-2 segments and metastasectomy refers to resection of metastatic nodule with negative margin or non-anatomic resection less than one segment or wedge resection. All the above mentioned surgical and nonsurgical factors thought to be related to overall (OS) and progression free survival (PFS) rates were statistically analyzed. This study was approved by the institutional review board of our institute (03.03.2015, 2015-5/9).

Operative mortality includes any deaths attributed to liver resection and all deaths within the 30 days after liver surgery. Deaths were ascertained by hospital records or official public records. For patients without evidence of disease, last date of any clinical correspondence was used to determine the length of progression free survival. Patients were categorized into six groups; Group 1: Breast cancer LM, Group 2: Gastric cancer LM, Group 3: Gastrointestinal stromal tumors (GIST) LM, Group 4: Pancreas cancer LM, Group 5: Genitourinary (GU) tumors LM and Group 6: Miscellaneous tumors (esophagus, melanoma, lung, peripheral nerve tumor, peritoneal mesothelioma, thyroid, adrenocortical) LM.

Statistical Analysis

Statistical analysis were done with SPSS 22 (IBM Corp, Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY9). Categorical variables were summarized with percentage. Variables were expressed as mean ± standard deviation or as median (minimum: maximum, range) values depending on whether the variable followed a normal distribution or not, using the Shapiro-Wilk normality test. The log-rank test was used to determine the difference between Kaplan-Meier curves for both OS and PFS time. Mean survival time was reported. To determine the prognostic factors that affected OS and PFS time, Cox proportional hazard regression analysis with backward selection procedure was performed after Kaplan-Meier analysis. Results were reported as hazard ratio with 95% confidence intervals (CI) and related p-values. Statistical significance was defined as $p< 0.05$.

RESULTS

There were 125 patients in the study period. Median age at the time of surgery was 58.42 years (range 26-86). The patients included were 56 (44.8%) males and 69 (55.2%) females. Most of the cases were LM of breast (n= 33, 26.4%), gastric (n= 25, 20.0%) and GIST (n= 16, 12.8%). Interval from resection of primary tumor to the diagnosis of liver metastases was 20.90 ± 28.9 (0-144) months. Mean number of metastases was observed to be 1.59 ± 1.0 (1-8) and mean diameter of the tumors was 3.9 ± 2.8 cm (1-18). Demographic data and other tumor characteristics are shown in Table 1. A total of 77 (61.6%) cases were metachronous and 48 (38.4%) were synchronous LM. The patients were categorized into six groups according to the type of primary tumor, and the distribution of the patients in each group is displayed in Table 2.

Operative Intervention

Major hepatectomy was performed in 20 (16.0%) cases and segmentectomy (n= 13, 10.4%) and metastasectomy (n= 92, 73.6%) were preferred in the remaining cases. Re-resection was performed in 9 (7.2%) patients when time interval between occurrence of two metastases was at least one year (breast 2, GIST 3, ovary 2, gastric 1 and lung 1).

Table 1. Demographic features of the patients	
Features	**n (125)**
Male/female (n)	56/69
Age (mean ± SD)	58.42 ± 10.78
Presentation (n)	
Synchronous	39
Metachronous	54
Tumor size (mean ± SD)	3.89 ± 2.8
Tumor number (mean ± SD)	1.59 ± 1.03
Interval (month)*	20.90 (0-144)
Resection type (n)	
Metastasectomy	92
Segmentectomy	13
Lobectomy	20
Re-operation (n)	9

*Median interval time from primary tumor surgery to diagnosis of liver metastasis.
SD: Standart deviation.

Table 2. Distribution of the patients according to the type ofprimary tumor

Breast	Gastric	GIST	Pancreas	GU (n= 16)	Miscellaneous (n= 17)
33	25	16	11	Renal cell= 8	Lung= 3
				Ovarian= 9	Mesothelioma= 1
				Endometrium= 3	P. nerve= 1
					Thyroid= 1
					Melanoma= 6
					Adrenocortical=1
					Esophagus= 2

*GIST: Gastrointestinal stromal tumor, GU: Genitourinary tumors, P: Peripheral.

Outcome

There were no operative mortality in this series and the mean length of hospital stay was 6 (2-70) days. Postoperative complications were developed in 13 (10.4%) cases. These were deep incisional surgical site infection in 4 (3.2%) of the cases, organ/space infection in 4 (3.2%) of the cases, anastomotic leakage in 2 (1.6%) of the cases (in concomitant surgery cases), bile leakage in 1 of the cases (0.8%) and iatrogenic small bowel perforation in one of the cases (0.8%). The median follow-up time was 21 (1-132) months.

Age, sex, re-resection, interventional radiologic treatment modalities, size and number of metastatic nodules, metastases interval and receptor status (for breast cancer liver metastases) were not determined as significant factors for both OS and PFS. Surgical margin status and chemotherapy after liver resection parameters were not available for statistical analysis due to insufficient sample size in each category. Factors associated with OS and PFS are shown in Table 3,4. LM from primary breast cancer had the longest OS and PFS. Pancreatic cancer, miscellaneous cancers and gastric cancer group significantly have shorter OS than the other groups. Tumor recurrence (metastases recurrence) was also found to be a significant risk factor for OS. The factors affecting OS were found to be type of primary tumor (pancreas group is the worst and breast cancer group is the best. p= 0.001), simultaneous surgical interventions with hepatectomy (p= 0.031) and development of surgical complications (p= 0.001) (Table 4). When all NCRNNE-LM patients were examined, the highest number of cases was breast cancer (33/125).

In terms of subgroup (breast, GIST, gastric, GU, pancreas and miscellaneous) analysis, there were not any factors shown to be associated with OS in all the groups except GIST. Univariate analysis revealed that patients having synchronous metastases had longer OS than those with metachronous metastases in

Table 3. Univariate analysis of the factors associated with survival for all cases

Features	n	Mean OS	p	Mean PFS	p
Type of primary tumor					
Breast	33	83.6 ± 13	*0.001*	56.8 ± 14	*0.008*
GIST	16	62 ± 12		32.5 ± 5	
GU	16	42.6 ± 7		31.6 ± 7	
Gastric	25	32.6 ± 7		34.6 ± 8	
Miscellaneous	17	24.65		15 ± 5	
Pancreas	11	12.3 ± 1.8		6.2 ± 1.1	
Synchronous/Metachronous					
Synchronous	48	41.9 ± 7	0.07	19.9 ± 3	0.02
Metachronous	77	61.5 ± 6		52.7 ± 9	
Concomitant procedures					
Yes	62	40.2 ± 7	*0.03*	21 ± 4	*0.01*
No	63	61.1 ± 8		51.1 ± 8	
Postoperative complications					
Yes	13	18.1 ± 5	*0.001*	18.2 ± 6	0.16
No	112	58.6 ± 5		43.3 ± 6	

GIST: Gastrointestinal stromal tumor, GU: Genitourinary cancer, OS: Overall survival (month), PFS: Progression-free survival (month).

Table 4. Cox proportional hazard regression analysis of the risk factors related OS and PFS

	OS		PFS	
Features	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Primary tumors				
Pancreas cancer	4.32 (1.3-13.7)	0.013		
Gastric cancer	4.08 (1.6-10.1)	0.003		
Recurrence	3.43 (1.6-7.1)	0.001		
Type of resection				
Metastasectomy			6 (1.4-25.1)	0.012
Segmentectomy			5.8 (1.8-29)	0.031

PFS is shorter in patients with metastasectomy and segmentectomy than lobectomy. OS is shorter in pancreas and gastric tumors with reference to breast cancer liver metastases, OS: Overall survival (month), PFS: Progression-free survival (month), CI: Confidence intervals, HR: Hazards ratio.

GIST cases (p< 0.03). On the other hand, lobectomy had more advantages on PFS as compared to metastasectomy in breast cancer LM cases (p= 0.01, HR= 8.41) (Table 4). Other risk factors were not found to be statistically significant for PFS in other groups. Receptor positivity (estrogen and progesterone) was also not found to be a statistically significant factor on OS and also PFS in breast cancer LM cases.

DISCUSSION

Liver is a quite eligible site for tumor cells to grow because of its specific type of blood flow which is provided by two different vascular systems including both portal system and arterial system. Therefore, it is not surprising that liver is the most commonly involved metastatic organ for all types of cancers. Liver metastases have been demonstrated in 58-79% of all the terminal period cancer patients and almost 85% of these have been found to be due to non-colorectal cancers in an autopsy study (8).

Although previously liver metastases were accepted to be one of the inoperability criteria, currently it is one of the main topics of hepatobiliary surgery. However, there are not enough multicenter, randomized controlled trials to build up a consensus about treatment algorithm of NCRNNET-LM. Most of the studies have been presenting data from single centers, retrospectively. Fortunately, the data in the literature is increasing in accordance with the improvements in hepatobiliary surgery and oncology together with the opportunity of simultaneous usability of alternative treatment modalities with surgery. Liver resection for NCRNNET-LM rate is less than 10% of the all hepatic resections due to isolated metastases which are relatively rare. Surgical treatment indications for these kinds of tumors have been extended depending on the development of surgical technics and management in an acceptable mortality and morbidity rate. In a large sample sized multicentric study, it has been determined that five-year survival rate is more than 30% in adrenal, ovarian, breast and renal cancer LM, 15-30% in gastric, pancreas, melanoma and duodenal cancer and less than 15% in lung, esophagus, head and neck tumors (9). On the other hand, five-year survival rate after surgery of CRC-LM, which has been proven to be most advantageous for survival, is reported as 40%-70%. In our series, mean survival time was 37.4 ± 4.3 months and median survival time was 28 (21-45) months in 60 patients who underwent CRC-LM. Therefore, it is possible to infer that the results of present study are acceptable, satisfying and encouraging. Also, the complication rate reported in the present study is within the acceptable limits.

In the present study, the group with most patients was the breast cancer group. In breast cancer, metastatic liver disease is generally associated with disseminated disease and prognosis is poorer when compared to bone or other soft tissue metastases. Only 5-12% of patients were found to have isolated liver metastases. In our study, breast cancer LM group had the longest OS and PFS. Mean (median) OS and PFS were 83.6 and 56.8 months respectively. These results are comparable to other studies (9-11). In the present study, it was found that in patients who had undergone lobectomy because of primary breast cancer progression free survival period was longer. While progression free survival was 23.6 ± 5.1 months in metastasectomy group, it was observed to be 107.4 ± 22 months in lobectomy group. According to Cox regression analysis when metastasectomy was chosen as a resection method the risk of shorter survival periods was observed to be 8.4 times higher. Therefore, lobectomy should be always kept in mind as a treatment modality despite it is a major surgical procedure. Additionally, in patients who are not appropriate for surgical procedures, treatment modalities such as RFA and TACE can be used. In several studies investigating case series, interventional radiological procedures were shown to be used successfully in metastatic liver disease originating from breast cancer and median survival was reported between 30 and 60 months (12). Receptor positivity and good response to chemotherapy were found as factors related to longer survival in breast cancer LM in one study (13). However, the current study does not support these findings with a relatively small number of cases.

The role of surgical resection of gastric cancer (GC)-LM has always been debated. Resectable metastases without extrahepatic disease have been reported to be present in only 0.5-10% of patients (14). Solitary disease and well differentiated primary tumor were other factors found to be associated with long term survival (15). There is not a consensus about indications and patient selection criteria for hepatectomy (16). There are studies in the literature indicating that gastric cancer-LM that can be resected R0 and sometimes the use of RFA is safe and appropriate. In this figure, the median survival was determined as 48 months (17). In our study, after breast cancer, the second most common liver metastasis was observed in gastric cancer. Mean overall survival was 32 months. Accordingly, it was observed that the overall survival was statistically significantly prolonged especially in patients with solitary liver metastases who were removed as mastectomy, which was consistent with the literature (15,18,19).

Stage 4 pancreatic adenocarcinoma has a poor prognosis and five-year survival is nearly 1% (20). Although a significant increase in survival has been achieved with the development of medical treatments, surgical treatment is still an important treatment in terms of long-term survival (21). The value of synchronous metastasectomy in pancreas cancer was analyzed and median overall survival was observed as 10.7 months (7). Similarly, there were 11 primary pancreatic cancer cases in our study, and the lowest PFS durations (6.2 ± 1 months) and the worst prognosis (12.3 ± 1.8 months) were among these patients. Furthermore, in this study three-year survival rate was showed to be 0% and surgical treatment does not provide any advantages on survival in patients with stage four pancreas cancer. The benefit of surgical treatment for this group, which has the least survival compared to other groups, is also controversial.

For stage 4 renal cell carcinomas, one-year survival rate has been reported to be 10-15% previously. However, treatment in those cases is more successful currently. In a study analyzing 43 patients with metastatic liver disease due to renal cell carcinoma, who underwent curative hepatectomy, were evaluated. They found that one and three-year survival rates were 94.2 and 62.1%, retrospectively (22). The criteria that should be considered in patient selection can be sorted as such: Curative surgical interventions to have negative surgical margins, interval >24 months, tumor size <5 cm and eligibility for repetition of hepatectomy (23). In our study, isolated liver metastases are encountered quite rarely in gynecologic cancers since liver metastases are generally a part of general tumor dissemination (24). In liver metastases of ovarian cancer, hepatectomy can be applied securely. Survival is better in cases where involvement is through peritoneal seeding when compared to hematogenous dissemination (23). The interval between the primary surgery (<24 months) and optimal secondary cytoreduction (residual disease of less than 1 cm) was found to be significantly associated with the longest survival periods in patients with liver resection during secondary cytoreduction (25). According to our data, OS was 42.6 ± 7.4 months and PFS was 31.6 ± 7.6 months for patients with LM due to GU malignancies. Although our survival times seem to be shorter when compared to the studies mentioned above, it may not be appropriate to make an inference based on data retrieved from such a heterogeneous patient group including renal cell carcinoma, endometrium and ovarian cancers.

In patient with LM due to malign melanoma survival is significantly poor and it was reported to be almost 15-20% (25,26). Contrary to cutaneous melanoma which primarily invades lymph nodes, in 95% of the metastatic uveal melanomas, liver metastases can be determined (27). In a study, similar survival periods have been observed in cutaneous and uveal melanoma cases (28). In our study, miscellaneous group including malign melanoma has the second worst survival rates following the GI group. According to our observations, laparoscopic exploration in case of LM due to malign melanoma gives more information about macroscopic features and subcapsular involvement because of staining pattern as compared to other tumor metastases.

In a study that investigated LM cases due to GIST, while median survival was found to be 53 months in patients given only imatinib, it was found to be 89 months in those who were given tyrosine kinase inhibitors (TKIs) in combination with liver resection (29). Likewise, concomitant therapy is suggested to be the therapy of choice by the Japanese study group (30). We found survivals following hepatic resections in combination with TKI therapy at first third and fifth years 76.2, 59.2 and 50.8 months respectively. Overall survival was shown to be 62.08 ± 12.9 months. We observed that the second-best OS and PFS periods following breast cancer were achieved in LM of GIST group.

In our study, re-resection was performed in seven patients when time interval between occurrence of two metastases was at least one year. Two of our patients with GIST are still being followed without recurrence for eight and 10 years. Although currently there is not a consensus about re-resection, surgical treatment modalities should be considered insistently in biologically good behaving tumors.

We can state as a limitation of our study the small sample size. However, this is an inexorable fact. In present study, since we share our experience in these relatively rare cases, we believe that this study could provide a contribution to the literature. However, larger sample sized more series are required to evaluate the effectiveness of surgical procedures in liver metastases of other cancers. On the other hand, the fact that it is a heterogeneous group study since it includes different tumor groups and biology is also limiting. However, we think that this study may be valuable in terms of sharing experience, as it appears that liver resection provides an advantage to survival in some tumor groups, while it may be unnecessary in others.

Ethics Committee Approval: This study was obtained from Uludağ University Faculty of Medicine Clinical Research Ethics Committee (Decision no: 2015-5/19, Date: 03.03.2015).

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Kolorektal-nöroendokrin dışındaki tümörlerin karaciğer metastazlarının cerrahi sonuçları: Gerçekten değer mi, gerekli mi?

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ÖZET

Giriş ve Amaç: Kolorektal kanser ve nöroendokrin tümörlerin karaciğer metastazlarında cerrahi tedavinin etkinlik ve sağkalım açısından avantajlı olduğu bilinmektedir. Bu çalışmadaki amacımız primeri kolorektal veya nöroendokrin olmayan tümörlerin karaciğer metastazlarının cerrahi tedavisinin sonuçlarını belirlemektir.

Gereç ve Yöntem: Primeri kolorektal kanserli (KRK) veya nöroendokrin tümörlü (NET) olmayan karaciğer metastazlı toplam 125 hasta çalışmaya dahil edildi. Hastaların demografik özellikleri, tümörün histolojik özellikleri, primer tümörün rezeksiyonundan karaciğer metastazlarının ilk tanısına kadar geçen süre, karaciğer metastazlarının primer malignite ile eş zamanlı ve metakron ortaya çıkışı, rezeksiyon tipi, postoperatif komplikasyonlar, hastanede kalış süresi ve hayatta kalma analizi yapıldı.

Bulgular: Ortalama takip süresi 21 (1-132) ay idi. Ortalama sağkalım (OS) ve ortalama hastalıksız sağkalım (HS) sırasıyla 29,86 ± 2,4 ve 21,23 ± 2,1 aydı. Olguların primer tümörünün çoğunluğunu meme (n= 33, %26,4), mide (n= 25, %20) ve gastrointestinal stromal tümör (GİST) (n= 16, %12,8) oluşturmaktaydı. Primer tümörün rezeksiyonundan karaciğer metastazı tanısına kadar geçen süre 20,90 ± 28,9 (0-144) ay idi. OS ve HS oranları sırasıyla; bir yılda %78 ve %69, üç yılda %45 ve %38, beş yılda %32 ve %21 ve 10 yılda %3,2 ve %1,6 idi. Meme kanseri karaciğer metastazları en uzun OS ve HS'ye sahipti. Pankreas kanseri ve mide kanseri grubu diğer gruplara göre önemli ölçüde daha kısa OS'ye sahiptir.

Sonuç: Verilerimize göre meme ve GİST karaciğer metastazlarında sonuçlar daha iyi olup, pankreas ve malign melanom karaciğer metastazlarında cerrahi tedavinin yeri tartışmalıdır.

Anahtar Kelimeler: Karaciğer metastazları, kolorektal olmayan, nöroendokrin olmayan

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