Curative versus palliative surgical resection of liver metastases in patients with neuroendocrine tumors: a meta-analysis of observational studies

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Background: The role of surgical therapy in patients with liver metastases from neuroendocrine tumors (NETs) is unclear. In this study, the results obtained with curative or palliative resection, by reviewing recent literature and performing a meta-analysis, were examined.

Materials and methods: A systematic review and meta-analysis of observational studies published between January 1990 and October 2013 were performed. Studies that evaluated the different survival between patients treated by curative or palliative surgical resection of hepatic metastases from NETs were considered. The collected studies were evaluated for heterogeneity, publication bias, and quality. To calculate the pooled hazard ratio (HR) estimate and the 95% confidence interval (95% CI), a fixed-effects model was applied.

Results: After the literature search, 2,546 studies were found and, among 38 potentially eligible studies, 3 were considered. We did not find a significant longer survival in patients treated with curative surgical resection of hepatic metastases when compared to palliative hepatic resection HR 0.40 (95% CI: 0.14-1.11). In one study, palliative resection of hepatic metastases significantly increased survival when compared to embolization.

Conclusions: Curative and also palliative surgery of NETs liver metastases may improve survival outcome. However, further randomized clinical trials are needed to elucidate this argument.

Keywords: Liver metastases; palliative surgery; curative surgery; neuroendocrine tumors (NETs); overall survival; meta-analysis

Introduction

Neuroendocrine tumors (NETs) are a group of neoplasms with different clinical presentation and growth rates (1). Historically, NETs have been considered as rare tumors, representing approximately 0.5% of all malignant conditions. More recent series incorporating large prospective tumor registries (SEER) report on the linearly increasing overall incidence and changing spectrum of NET manifestation over the past four decades. Even being considered benign it is common to find these tumors in advanced stage often with liver metastases (2-7). Different medical and surgical treatments have been proposed for patients with liver metastases from NETs (3,8-10).

However, the exact role and real effectiveness of surgery for patients with liver NETs metastasis is still poorly defined considering, the frequent slow growth and long-term natural history of these tumors. This review was made to evaluate the survival impact of liver resection in patients with hepatic metastases NET's tumors.

Materials and methods

Search strategy for review

Three authors independently carried out a literature search by gathering information from Medline, Embase, Ovid, Google Scholar, and Cochrane database for studies

244

Bacchetti et al. Surgical resection of liver metastases

published form January 1990 to October 2013. Search terms included "neuroendocrine tumor" or "carcinoid tumor" or "gastrointestinal NETs" or "liver metastases" or "hepatic metastases" or "neuroendocrine metastases" and "hepatectomy" or "liver resection" or "liver transplantation". All the titles and the abstracts resulted from these queries were examined. We first selected all the articles that referred to the surgical treatment of liver metastases from NETs. Second, we analyzed the full articles. Third, we used bibliographies and citations from full articles and previous review publications to identify other additional pertinent articles.

Inclusion and exclusion criteria

All observational and experimental studies that evaluated survival in patients affected by NET liver metastases and treated by hepatic complete surgical resection or palliative surgical resection were considered. All included studies were observational (level III or IV of evidence, CEBM) (11) and no randomized trials comparing complete or palliative resections of liver metastases have been found. We considered, in this meta-analysis, Kaplan-Meier curves or Cox proportional hazards regression models to calculate the survival difference among patients treated with palliative or complete resection of liver metastases. Moreover, we included only articles with the full text available for data retrieval that were performed on human subjects and written in English. We retrieved from full text articles time frame for NET diagnosis, geographic locations, and treatment in order to avoid any possible population overlap. The study of better quality or with more detailed data was included in case of two or more studies presenting possible data overlap. When discrepancies among the three reviewers were found, a joint reevaluation of the original article was performed to address them. Studies considering <20 patients, non-English written articles, or studies about nonhuman subjects were specific exclusion criteria. In addition, letters to the editor without original data, editorials, case reports, and reviews were excluded. Moreover, conference abstracts due to the lack of details regarding survival data and study design were excluded.

Data extraction

Three independent reviewers extracted data from the selected articles by using a predefined data extraction form. As previously described, any discrepancies in data extraction or unsuitability for inclusion were discussed (12) and the following information was extracted: authors, year of publication, geographical area, population characteristics (age, sex, etc.), study design, number of patients, type of procedure applied, hazards ratios with 95% confidence interval (95% CI), or hazards ratios (HRs) extracted from Kaplan-Meier curves. The HR was calculated using methods previously described from data obtained from published reports (13).

Quality assessment for included studies

The quality of each included study was assessed by using the Newcastle-Ottawa Scale. We defined studies of high quality those that scored nine or eight points on the Newcastle-Ottawa Scale and studies of medium quality those that scored seven or six points. Discrepancies in quality assessment were solved as previously described (12).

Data analysis

Data was analyzed by R (version 3.0.1), considering significant the P<0.05. We calculated a summary statistic considering the hazards ratio for survival analysis. Rank correlation test of funnel plot asymmetry was used to test the presence of any publication bias (14,15). The I^2 index and the Cochran Q to assess the heterogeneity among studies were used. As previously described an I^2 index value >50% and, a Q statistic P value <0.10 were considered statistically significant signs for heterogeneity (16). We applied, where appropriate the fixed- and the random-effect model to calculate the pooled estimate. We reported the primary outcome in this meta-analysis as HR (with 95% CI) of overall survival in patients treated with complete hepatic resection of metastases. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for accurate performing meta-analysis of observational studies (17) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines checklist (18) were considered to prepare this meta-analysis.

Results

Search results

During the first stage of literature search we found 2,546 studies (*Figure 1*). In *Figure 1* is shown the literature search design: after reviewing the titles and abstracts we
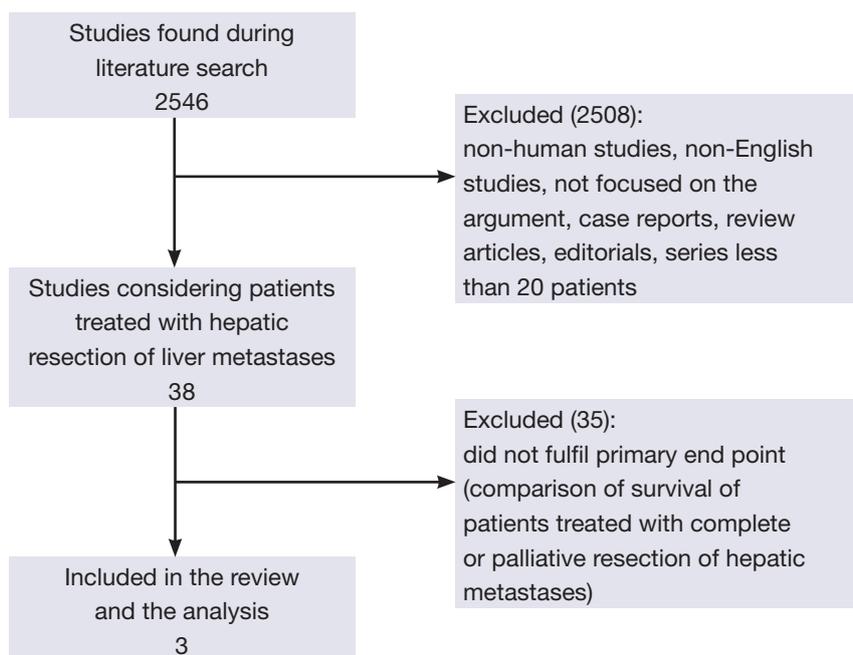
Figure 1 Flow-chart of the literature search and selection.

Table 1 Description of the included studies that considered curative *vs.* palliative intent of surgical resection

Labels	Location (city, country)	Publication year	Study period	Number of patients (liver resection: complete/palliative)	5-year OS
Osborne 2006	Tampa (USA)	2006	2000-2004	38 complete and 23 palliative	78% complete and 64% palliative
Chamberlain 2000	New York (USA)	2000	1992-1998	15 complete and 19 palliative	53% all
Que 1995	Rochester (USA)	1995	1984-1992	28 complete and 46 palliative	73% all (*)

*, 4-year OS. OS, overall survival.

found 2,259 articles to be not eligible as they were case reports, review articles, editorials, non-human studies or non-English articles, not focusing on the review topic, and others not meeting the inclusion criteria. A total of 38 articles as potentially eligible for this review were identified. A total of 35 of these articles either did not described the outcome differences between complete hepatic resections and palliative surgery (5,9,19-30) or did not reported any HR (31-41) or Kaplan-Meier curves to compare complete surgical resection of hepatic metastases with palliative resection of hepatic metastases (42-52). Therefore they were excluded. We finally selected three eligible articles that compared survival between patients treated by curative surgical resection of hepatic metastases and patients treated by palliative debulking surgery using Kaplan-Meier curves (*Figure 1*) (53-55). These included

research articles were found to be all observational retrospective studies.

Characteristics of the studies

In this meta-analysis we included three retrospective observational studies that evaluated survival in patients affected by NET comparing curative surgical resection of hepatic metastases with palliative surgical resection (*Table 1*) (53-55). All the three included studies compared curative/ complete surgical resection with incomplete/palliative surgical resection.

In the paper of Osborne *et al.*, surgical exploration was undertaken when resection of at least 90% of the hepatic disease was feasible. In this study, the resections were defined as curative if the entire hepatic disease was
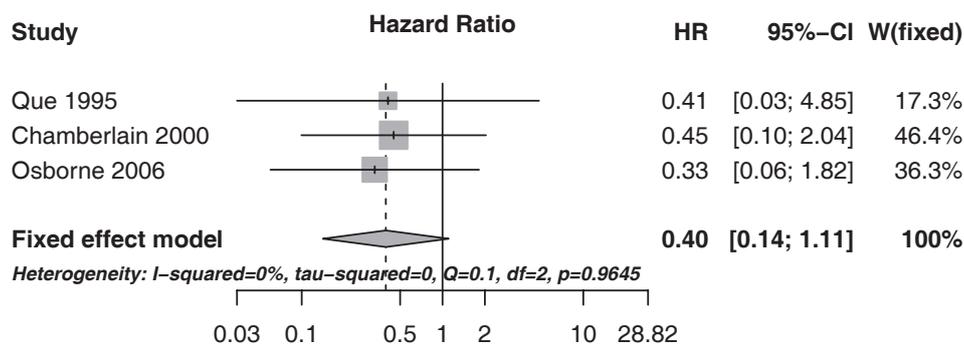
246

Bacchetti et al. Surgical resection of liver metastases

Figure 2 Forest plot of overall survival comparison between complete hepatic metastasis resection versus palliative hepatic metastasis resection.

removed or palliative if there was, after resection, evidence of gross residual disease. Tumors that were ablated with radiofrequency were considered curative when all gross disease was addressed. Osborne *et al.* compared also incomplete/palliative surgical resection of liver metastases with conservative treatments (embolisation) and they found that the survival difference when comparing palliative cytoreduction with embolization was significant (53).

In the analysis of Que *et al.*, resections were considered curative only if all gross primary, regional and hepatic extent, was resected and palliative when gross residual disease was present either intra-abdominally at operation or extra-abdominal by imaging.

Chamberlain *et al.* stated that resections were considered curative only if all gross disease was resected. In the other cases, palliative hepatic surgery for symptoms palliation was undertaken.

In *Table 1* the characteristics of the included studies are shown. The HR was extracted from Kaplan-Meier curves because none of the three included studies presented Cox proportional hazards multivariate regression models. All the excluded studies were observational (5,9,19-30) and retrospective (31-41) and HR extraction was not possible (42-52). The majority of these excluded studies were described and summarized by recent review articles (12,56).

Quality assessment of the included studies

The quality of the evidence about the influence of complete surgical resection in comparison to incomplete resection on survival of patients with NET liver metastases is low (levels III-IV, CEBM) (11).

All studies in our meta-analysis showed an increased survival in the groups treated with curative surgical

resection of liver metastases but none of the included studies was randomized. The three independent reviewers agreed that all studies were graded seven or six points according to Newcastle-Ottawa scale for quality (medium quality).

Main analysis

The meta-analysis was performed on the three selected studies, as shown in *Figure 2*. The included studies analyzed a total amount of 169 patients affected by NET liver metastases: 81 treated by radical surgery and 88 by palliative surgery. The I^2 index value was 0% and the Q statistic P value was 0.965 therefore we found no heterogeneity among the included studies and the fixed-effect model to calculate the pooled estimate was used. We found an increased survival, but not statistically significant, in the group of patients treated with complete surgical resection of hepatic metastases HR 0.40 (95% CI: 0.14-1.11) compared with patients who underwent only palliative resection (*Figure 2*).

Risk of bias assessment

All the included observational studies were classified as medium quality ones. The main limit to consider observational retrospective studies was that of a possible selection bias of different authors in considering patients suitable for curative surgery or palliative surgery of liver metastases. The article of Que *et al.* did not highlight the differences between the two groups (curative *vs*. palliative surgical resection), and it is also unclear whether in cases of palliative surgery the non-radical resection refers to the primitive tumor or the liver metastasis (55). In the article of Chamberlain *et al.*, there were no differences between radical and palliative surgical resection of liver
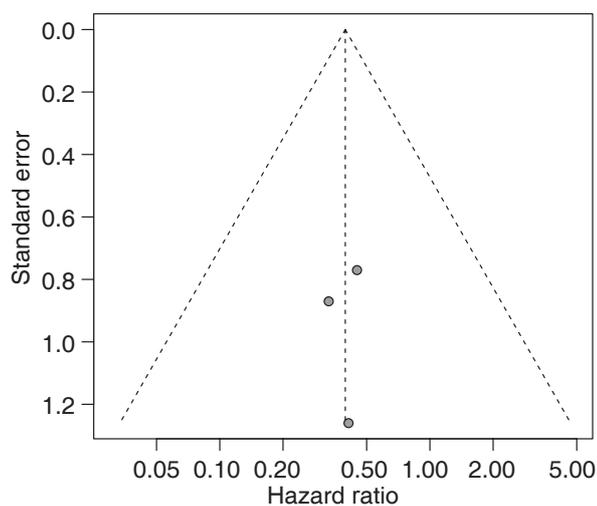
Figure 3 Funnel plot.

metastases with regard to gender, age, synchronous or metachronous presentation, tumor histology or location, indications for treatment, hormone secretion, or percentage of liver involvement. However, the two studied groups did significantly differ in terms of lobar liver involvement and the majority of bilobar disease involvement underwent palliative surgical resection of liver metastases (54). The study of Osborne *et al.* did not showed the possible differences in pre-treatment status between radical and palliative surgical resection of liver metastases (53).

Publication bias

The presence of a possible publication bias was examined (*Figure 3*). These results should be considered with caution, because our meta-analysis calculation included only three studies (*Figure 2*). Anyway, none of the studies seems to be out of the symmetry in the plot (*Figure 3*). As a consequence, the rank correlation test of funnel plot asymmetry had a P value of 0.908. However, the current guidelines do not recommend testing for the funnel plot asymmetry or for the correlation test of funnel plot asymmetry in analysis of a limited number of studies (<10) (57,58).

Discussion

Recent data demonstrate that the incidence of NETs has increased exponentially (overall 500%) over the last three decades (59). In an analysis on 13,715 patients, Modlin stated that in 12.9% of all carcinoid patients, distant

metastases were already evident at the time of diagnosis and the overall 5-year survival rate for all carcinoid tumors was 67.2% (60). These findings bring into question the widely promulgated benignity of these neoplasms and now many clinicians think that all NETs should be considered to have potential malignancy (61-65). The occurrence of hepatic metastases is one of the most important prognostic factors for NET's survival (3,42,54,66), but still now, considerable controversy exists concerning how to approach patients with neuroendocrine metastases. The management of these patients varies from control of symptoms to more aggressive surgical or radiological therapies. For patients with non-resectable liver disease, treatments like bio-therapy with somatostatin analogues, radio-peptide receptor therapy, transarterial chemoembolization, selective intra-arterial radiotherapy or new molecular target-directed therapy can be performed (67-69). For localized hepatic metastases, surgical therapy appears the most efficient approach (8,9,27,42,66,70-72). A potential curative resection of liver metastases can be undertaken in 13.7-24.5% of the patients with advanced NETs (28,45,73). Symptomatic patients can be relieved with cytoreductive procedures, but the role of surgery, particularly if aggressive, is more debated for patients with asymptomatic disease. To complicate the problem of the best therapy for patients with metastatic NETs, many studies reporting the outcome following surgical management of liver metastases focused solely on resection rather than combined-modality approaches.

The survival impact of hepatic resection is difficult to assess also for other reasons. First, the patient selection criteria differ in many centers and, in several studies, the completeness of resection was not clearly determined. Second, most studies give analysis of pooled data of uncleared primary site of NETs from forgut, midgut and hindgut origin. Third, the results of surgery or other therapies have often not been determined separately in the absence of prospective randomized controlled trials (RCTs) and therefore recommendations have to rely only on recently published retrospective series.

The published studies suggest that surgical resection of hepatic neuroendocrine neoplasms can be associated with favorable survival, but clinical and oncologic variables that can distinguish patient cohorts taking advantage from such aggressive therapy have not been identified. Also being not available RCTs evaluating patients with liver metastases from NETs, the question of effectiveness of other treatment modalities such as RFA, chemoembolization or use of Yttrium-90 micro-spheres remains unsolved.

All studies in our meta-analysis showed an increased survival in the groups treated with complete surgical resection of liver metastases, but none of the included studies was randomized (53-55).

Few studies have been designed to evaluate the impact of non-surgical therapy. Osborne *et al.* compared the difference between surgical therapy versus embolization and concluded that surgery is superior to embolization for symptom control and also found that palliative resection of liver metastases had a better survival than embolization (53).

Crucial questions remain unsolved. What kind of palliative treatment should be chosen facing non-resectable NETs liver metastases, in hopes to achieve prolonged outcomes and palliation? Which is the role of liver surgery in down-staging hepatic metastases extent allowing other non-surgical therapies to control the liver disease? How to accurately assess the full extent of metastatic disease in order to select the proper surgical management of patients with NET, particularly when considering transplant candidates?

Following full-text evaluation of 38 articles potentially eligible for this review, 35 of them did not described the outcome differences between curative hepatic resections and palliative surgery or did not reported any HR or comparison by Kaplan-Meier curves. Therefore a total amount of 169 patients affected by NET liver metastases, 81 treated by curative surgery and 88 by palliative surgery, were considered. In this meta-analysis, even if the number of studied cases is limited, curative resection of liver NETs metastases showed a non significant increased survival compared to palliative surgical resection HR 0.40 (95% CI: 0.14-1.11). Unfortunately, the results of our review does not allow definite answers but, taking into consideration this outcome and the concordant increased survival recorded in all patients treated with surgical resection of liver metastases (12), a curative and even palliative resection of neuroendocrine liver metastases should be considered in order to improve patient's survival.

Conclusions

Liver metastases are frequently encountered in patients with NETs. For patients with resectable hepatic disease, the majority of the authors indicate liver resection, as this treatment results more likely to offer the best long-term outcome. All patients should be considered for curative surgical treatment but also palliative resection of liver metastases can be suggested. The advantage that can be potentially achieved with surgery, is that of removing all gross disease. Since there are no randomized clinical trials confirming clear advantages of hepatic resection, no definite conclusion on the impact of this aggressive approach can be achieved. However, basing on the results of this meta-analysis, palliative surgery, especially in patients with symptomatic disease, has a positive role (if at least 90% of the gross disease can be resected). In the future, new clinical and biological prognostic factors could be of help for the better identification of those patients who might benefit from hepatic surgical therapy.

Acknowledgements

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250

Bacchetti et al. Surgical resection of liver metastases

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