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Review Article

Liver Cytoreduction Threshold In Metastatic Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs): Systematic Review of Current Literature

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Abstract

Background: There is no universal agreement on the optimal degree of cytoreduction in metastatic Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs). This systematic review will summarize the current data for different thresholds of liver debulking surgery in GEP-NETs.

Methods: We conducted a systematic review for clinical benefit from different thresholds of liver cytoreduction surgery (≥90% vs >70%) in patients with metastatic GEP-NETs. We summarized clinical outcomes and different factors that impact outcome. We excluded studies that did not include clear liver cytoreduction threshold, and studies that did not report a direct correlation between liver debulking and primary outcome.

Results: 12 articles were included for final analysis. ≥90% cytoreduction studies were associated with longer PFS than those with 70% cytoreduction (45.6 - 56 months vs 20.6 - 36 months). Only two studies compared both thresholds and reported longer PFS (56.1 vs 20.6 months, P < 0.01, and 4.4 yrs vs 1.3 yrs, p=0.05 respectively) associated with ≥90% cytoreduction. Two studies compared OS between both cytoreduction thresholds with no significant difference (p = 0.6 and 0.29). Both cytoreduction thresholds were associated with 5-year recurrence rates of greater than 90%. Improved outcomes were found in patients with lower tumor grade (G1, 2) and lower liver tumor burden (<25%).

Conclusions: Although 90% cytoreduction threshold may be associated with improved PFS compared to 70% cytoreduction threshold, review of the current data did not demonstrate overall survival differences. Tumor grade and liver tumor burden seem to impact outcomes. With the current lack of prospective trials, knowledge gained from the review of the retrospective data can help guide individual patient management decisions regarding appropriateness for liver debulking surgery in metastatic GEP-NETs.

Keywords: Cytoreduction; Liver; Metastasis; Neuroendocrine Tumors;

Introduction

Neuroendocrine Tumors (NETs) are heterogeneous neoplasms that can originate in numerous organs include the gastrointestinal tract [1]. In the last decade, there has been a more than six-fold increase in the annual incidence of NETs due to a variety of factors including heightened awareness by physicians, significant progress in pathological and imaging techniques, and an increase in endoscopic surveillance [2]. Gastroenteropancreatic NETs (GEP-NETs) account for 70% of NETs, and most commonly metastasize to the liver [3]. In fact, liver metastases are the most common cause of death in patients with GEP-NETs. The treatment of GEP-NETs requires multidisciplinary management and decisions are influenced by tumor differentiation, grade, liver tumor burden, presence of extrahepatic metastases, and patient comorbidities. In patients with localized disease, complete surgical resection offers the only potentially curative option. But for patients presenting with recurrence and advanced-stage disease, extensive hepatic disease burden is not an uncommon scenario. In contrast to many other cancers, the presence of liver metastases in GEP-NET patients does not preclude surgical treatment. Furthermore, surgical resection can be performed in a cytoreductive strategy even if all disease cannot be completely resected. Multiple retrospective studies have demonstrated that the cytoreduction of liver metastases is associated with improvement of endocrine-related symptoms as well as survival [4-10]. However, the degree of liver cytoreduction remains an area of debate. Historically, a threshold of cytoreduction of ≥90% or more of liver metastases has been targeted and shown to be associated with improved outcomes in patients with GEP-NETs [7,11]. More recently, some studies have proposed that surgical resection of 70% or more of liver metastases may also contribute to improved Progression Free Survival (PFS) and symptomatic relief [9,10,12]. Given the lack of prospective data, the degree of cytoreduction remains a controversial area where the level of evidence to relax the cytoreduction target is insufficient and requires further investigation. Therefore, we conducted a systematic review to summarize the current data regarding cytoreduction thresholds and their correlation with other factors including liver tumor burden, removal of primary tumor, grade, and functionality.

Methods

We performed a systematic review of the literature using PubMed, Medline, Cochrane CENTRAL, Embase, the National Institutes of Health trial registry, and published proceedings from major oncologic and gastrointestinal cancer meetings include (ASCO, GI-ASCO, ESMO, ENETs, NANETs, SNMMI). A professional medical research librarian searched from 1990 through December 2020 for retrospective and prospective data related to liver cytoreduction in neuroendocrine tumors. Key search terms were liver cytoreduction, debulking surgery, neuroendocrine tumors. Publications were limited to clinical trials published in English. The results were imported into EndNote, and duplicate references were eliminated. Two authors (A.M. and S.W.) independently reviewed all search results and together determined publications that met the criteria for study inclusion. Studies that did not include GEP-NETs, did not report clinical outcome, or did not specify cytoreduction threshold were excluded. After determining which articles were relevant, the same authors independently extracted all the clinical data. Then both authors reviewed the collected data and summarized it accordingly. Because the outcomes were extremely heterogeneous between these collected studies, we could not perform meta-analysis for the collected data, and instead we summarized the data to answer important clinical questions such as the impact of different cytoreduction thresholds on clinical outcome (PFS, OS, RR), effect of liver cytoreduction on symptom relief and biochemical response, factors that may impact the benefit from liver debulking surgery (liver tumor burden, primary tumor and grades), and if there were differences in post-operative complications and incidence of carcinoid crisis between different cytoreduction thresholds. After summarizing all the data, two reviewers (A.M. and S.W.) also independently evaluated data according to whether findings from each study was clearly correlated with ≥ 90%, or 70% cytoreduction and which studies compared the two thresholds.

Results

Our initial search identified 968 articles from four databases and scientific conferences. 7 articles were automatically eliminated because they were exact matches, and 442 were manually identified as duplicates and removed, leaving 519 articles. We retrieved these articles and reviewed them for preset inclusion criteria. 12 articles reporting on 2146 patients met the inclusion

criteria for final analysis and review (Figure 1). All the included data were retrospective. We summarized the collected data for both cytoreduction thresholds to answer the following clinical questions:

- Is ≥ 90% liver cytoreduction a strict cutoff for better outcome?
- Are both cytoreduction thresholds associated with symptom relief and biochemical response?
- Does liver tumor burden impact cytoreduction outcome?
- Should primary tumor origin determine the appropriate liver cytoreduction threshold?
- Should grade affect cytoreduction threshold?
- Are there significant differences in post-operative complications and carcinoid crisis between both cytoreduction thresholds?

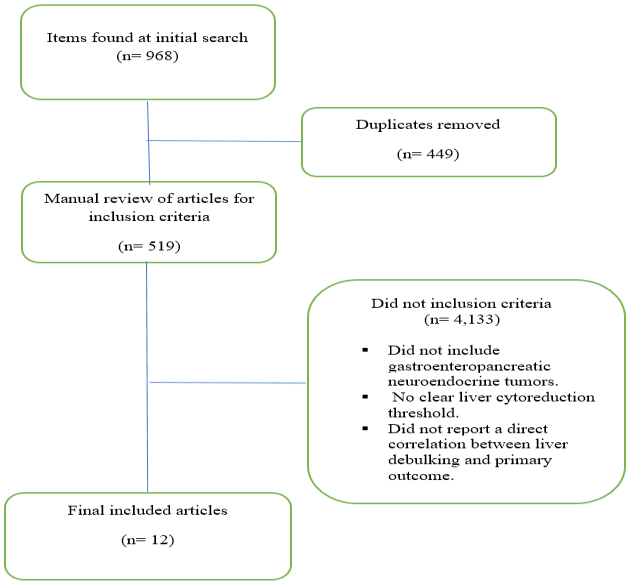

Figure 1: Flow chart of study selection.

Is ≥ 90% Liver Cytoreduction A Strict Cutoff for Better Outcome?

There are numerous retrospective studies suggesting that surgical cytoreduction of liver metastases in GEP-NETs may be associated with symptom control and prolonged survival. This is achieved as it "resets the clock" by removing most or all the grossly visible disease, leaving a patient with microscopic or a small amount of macroscopic disease, therefore delaying tumor progression. Although the optimum management is complete surgical resection of the primary tumor and all the liver metastases, NET liver metastases are commonly extensive and bilobar which precludes R0 resection. The original accepted threshold was 95% and then was reduced to 90% as retrospective data showed associated improvement in both symptoms and survival rate [13]. In addition, there are other studies suggesting that 70% debulking of liver metastasis is associated with improved outcome and may be considered a reasonable target for palliative cytoreduction [9,10,12]. Currently, there is no universal acceptance of either 90% vs 70% cytoreduction given that all data are exclusively retrospective, and the chosen percentage was not based upon comparison of outcome between the different levels of liver cytoreduction.

Progression Free Survival (PFS) and Overall Survival (OS)

Four of the twelve studies which included 388 patients with GEP-NETs reported improvement in PFS with palliative liver cytoreduction [8,10,12,14]. The median PFS ranged between 45.6 - 56 months for those who had ≥90% cytoreduction, while the PFS ranges between 20.6 - 36 months for the 70% group. Two of these studies compared ≥90% to 70% cytoreduction, Scott et al. and Maxwell et.al., reported significant improvement in PFS with ≥90% vs 70% cytoreduction (56.1 vs 20.6 months, $P < .01$, and 4.4 yrs vs 1.3 yrs, $p=0.05$, respectively) [12,14]. Among the studies included in our review, ten reported different survival endpoints including median overall survival (OS) as well as 5- and 10-year overall survival rates (SR). [4-10,12,15,16] (Table 1) Six of these ten studies reported significant improvement in median OS with both ≥90% and 70% palliative cytoreduction compared to historical controls (range: 80-275 months and 75-148 months respectively [4-7,12,15]. The 5-year survival ranged between 61-88% for the ≥90% cytoreduction group and 56-74% for the 70% cytoreduction group [5-10,16]. Only three studies reported 10-year SR, which was 35-76% for ≥90% cytoreduction and 28-41% for the 70% group [5-7]. Moreover, three studies compared the overall survival benefit for ≥90% vs 70% cytoreduction groups [5,8,15]. Woltering and colleagues reported improvement in median OS and SRs for ≥90% liver cytoreduction compared to the 70% group for both gastrointestinal and pancreatic NETs [5]. The median OS for patients with pancreatic NETs in this study was 80 months (95% CI 54-80 months) vs 75 months (95% CI 33-120 months). The 5, and 10-year SRs were (68% and 41%) vs (56% and 28%) respectively. For patients with small bowel NETs median OS was 275 months (22.9 years; 95% CI 201-275 months) vs 148 months (12.3 years; 95% CI 111-181 months). The 5, and 10-year OS rates were (87% and 76%) vs (89%, 64%) respectively. In contrast, Scott et.al. reported that ≥90% cytoreduction was not associated with improved median OS when compared with 70% (median not reached versus 134 months, $p = 0.6$). Similarly, a study by Morgan et.al. showed no difference in median OS (≥70% vs ≥90% $p=0.29$) [8,15].

Study	Cytoreduction Threshold	Primary tumor/Number	Sex/Age	Previous Systemic Therapy	Outcome (PFS, OS, SR)	Post-operative complications (Major)	Post-operative mortality
Que 1995	≥90%	pNET (23) and SBNET (50)	Men: 38% Median Age 55 years	SSA	4-year OS 73%	24%	NR
Sarmiento, 2003	≥90%	pNET (52) and SBNET (90)	Men: 43% Median Age 57 years	SSA Interferon CT	Median OS 81 months 5-year SR 61% 10-year SR 35%	14%	1.20%
Osborne, 2006	≥90%	pNET (16) and SBNET (36)	Men: 54% Median Age 56 years	SSA CT	OS 32 months	3.20%	1.70%
Chambers, 2008	≥70%	SBNET (59), Stomach (2), Appendix (1), Rectum(3)	Men: 62%, Median Age: 60 years	SSA	5-year SR 74%	22%	0%
Mayo, 2010	≥90%	pNET (137) and SBNET (180)	Men: 53.4% Median Age 54.9 years	SSA	PFS 1-year 56.9% 3-year 24.2% 5-year 5.9% OS 1-year 92% 5-year 74% 10-year 51%	NR	NR
Graff Baker, 2014	≥70%	SBNET (42), Appendix (1), Colon (1)	Men: 33% Median Age 57.8 years	Unknown	Median PFS 72 months 5-year DSS 90%	NR	NR
Bertani, 2015	≥90%	SBNET (49)	Men: 59% Median Age: 58 years	SSA PRRT	3-year SR 93.2% 5-year SR 82%	NR	NR
Woltering, 2016	≥90% vs ≥70%	pNET (89), SBNET (516)	Men: 46% Median Age 57.8	SSA PRRT Y-90 CT	OS 80 vs 75 mos 5-year SR 68 vs 56% 10-year SR 41 vs 28% 20-year SR 41 vs 40% OS 275 vs 148 mos 5-year SR 87 vs 89% 10-year SR 76 vs 64% 20-year SR 56 vs 25%	17% 12%	2%

Maxwell,2016	≥90% vs ≥70%	pNET (28) and SBNET (80)	Men: SBNET: 61.3% pNET: 46.4% Median Age SBNET: 60.3 years pNET: 54.7 years	SSA PRRT CT	pNET: - Median PFS: 52.8 vs 36 months SBNET- Median PFS: 45.6 vs 38.4 months	70-94%	0%
Morgan,2018	≥90% vs ≥70%	pNET (34) and SBNET (8)	Men: 52% Median Age 52	SSA Everolimus CT	Overall PFS 11 months Overall 5yr SR 80% 33 months PFS 50% vs 62% OS 88% vs 87%	18%	NR
Ejaz,2018	≥80%	pNET (254) and SBNET (188)	Men: 53% Median age: 57 years	CT	OS 87 months 5-year SR 60.7%	NR	NR

Annotations: CT: Chemotherapy; ST: Systemic Therapy; SSA: Somatostatin Analogs; PRRT: Peptide Receptor Radionuclide Therapy

Table 1: Impact of cytoreduction thresholds on outcome in GEP-NETS.

Recurrence Rate (RR)

Patients who had ≥90% liver cytoreduction were monitored through two studies for the risk of recurrence [6,7]. Mayo et al. and Sarmiento et al. reported a 5 year recurrence rate of 94% and 91% with median time to recurrence of 15.2 and 16 months respectively [6,7]. In the Mayo Clinic experience, after 43.3 months follow up, 199 of 339 (58.7%) patients had recurred and the 10-year overall recurrence was 99% [6]. However, there are no studies comparing the risk of recurrence between ≥90% and 70% liver cytoreduction groups.

Are Both Cytoreduction Thresholds Associated with Symptom Relief and Biochemical Response?

With advances in local and systemic therapies, surgical cytoreduction is not commonly required for symptom relief for GEP-NETs in the modern era. However, there is a body of literature examining this question which we have included in this systematic review. Six studies report results of the impact of cytoreduction on symptom relief for functional GEP-NETs. Four of these studies included patients who underwent ≥90% cytoreduction. Partial or complete symptomatic relief was reported in 93-100% of the patients [4,7,9,12,15,17]. Osborne et. al. report that 93% of the patients had symptom improvement, while 69% had complete symptomatic relief [4]. The median symptom-free interval was 56 months (44-71 months). The other three studies in the ≥90% group by Sarmeinto, Scott, and Que et.al. reported symptomatic relief in 96%, 60%, and 60% respectively [7,15,17]. The symptom recurrence rate was 59% at 5 years, with a median time to recurrence of 45.5 months. All four studies reported that subjective improvement of symptoms was associated with a reduction in levels of urinary 5-HIAA measured 6 to 12 months after surgery in 69-100% of the patients (from 585mg/24 hrs to 21mg/24 hrs, $p<0.001$) [7]. Two studies analyzed the impact of 70% cytoreduction on controlling symptoms and biochemical response with conflicting results [9,12]. Chambers reported that 75% (42/56 patients) had subjective improvement of symptoms, correlated with reduction in urinary 5HIAA level (from 400 micromol to 150 micromol 6-12 months after surgery) [9]. Meanwhile, Maxwell et.al. reported that 70% cytoreduction did not correlate with achieving either complete or partial biochemical response. ($p = 1.0$) [12]. Only one of the six studies compared the impact of different cytoreduction thresholds on both symptoms and biochemical response. Although results showed improvement in symptoms with ≥90% vs 70% cytoreduction (60% vs 42%, p 0.03), this was not associated with biochemical response (68% vs 71%, p 0.88) [15].

Does Liver Tumor Burden Impact Cytoreduction Outcome?

Several studies have shown that survival benefits of different liver cytoreduction thresholds (≥90% and 70%) was mainly for patients with lower liver tumor burden, defined as <25% of total liver volume. In one study, Bertain et al. reported a longer 5-year

Disease-Specific (DSS) and overall survival in patients who had at least ≥90% liver cytoreduction and had presented with lower liver tumor burden [16]. In that cohort, 5-year DSS for patients with liver tumor burden <25% was 91.3% compared with 74.6% for those with 25-50% involvement and 50.0% for those with >50% involvement (p= 0.001); the corresponding 5-year OS rates were 88.6%, 74.6%, and 50% (p< 0.001) respectively. In another study by Ejaz et al. of 612 NET patients, those with less than 50% hepatic involvement had a longer median survival (<50%: not reached vs. >=50%: 128 months; P < 0.001) [18]. After stratifying by extent of liver metastatic disease, patients with <50% tumor burden who underwent liver cytoreduction tended to have a longer median OS than those with higher tumor burden (89 months vs. 55 months, p = 0.14). Maxwell et al. reported that 70% cytoreduction in patients with small bowel NETs and liver tumor burden < 25% was associated with a significant improvement of PFS but not OS compared to those with small bowel NETs and >25% tumor burden (PFS 3.2 years vs 1.9 years, p=0.02, OS not reached vs 9.1 years, p =0.14) [12]. Overall, the data support the hypothesis that the outcome benefit of liver cytoreduction is mainly in patients with low liver tumor burden defined as <25%. Therefore, selection criteria should include consideration of liver tumor burden in addition to the current exclusion criterion of extrahepatic metastases because there is no current evidence that patients with high liver tumor burden have survival benefit over systemic therapy.

Does Primary Tumor Origin Determine the Appropriate Liver Cytoreduction Threshold?

The survival benefit of cytoreduction of liver metastasis has been reported in patients with midgut and pancreatic NETs, and the results differ based on the primary site. In a study conducted by Woltering et.al., small bowel and pancreatic subgroups had a comparable survival benefit with no significant differences following both ≥ 90 and <90% liver cytoreduction [5]. Compared to <90% cytoreduction, patients with small bowel NETS who underwent ≥ 90% cytoreduction had improved median OS, 10 and 20 years SR (275 mos vs 148 mos, 76% vs 64%, and 56% vs 25%, respectively). Pancreatic NETs had similar results with improvement in median OS, 5-, 10-, and 20-year SR compared to those with <90% liver cytoreduction (80 mos vs 75 mos, 68% vs 56%, 41% vs 28%, and 41% vs 40%, respectively). Although small bowel NET patients were reported to have greater survival benefits with both ≥ 90 and <90% cytoreduction than those with pancreatic NETs, there were differences in post-surgical life expectancy between the groups and the study did not directly compare them. The report by Sarmeinto, et.al., indicated that patients who had ≥ 90% liver cytoreduction demonstrated no significant difference in either 5 year SR or median OS among patients with small bowel vs pancreatic tumors (62% versus 61%, and 87 months versus 66 months, respectively; p = 0.58) [7]. Moreover, a study by Mayo, et al., showed that neither small bowel primary nor pancreatic NET primary tumor histology was associated with increased risk of recurrence in those who had >90% cytoreduction (p = 0.076) [6].

The data are even more limited in those with 70% cytoreduction. Scott, et.al, reported that resection of the primary tumor was significantly associated with improvement in PFS (HR 0.61, p=0.02) but not OS (HR 1.09, p=0.81) in those who had at least 70% liver cytoreduction [15]. In addition, in studies conducted by Maxwell et.al and Scott et.al., the authors report a survival benefit compared to historical control of both cytoreduction thresholds (≥ 90 and 70%) with no significant difference among small bowel vs pancreatic NETs (median PFS 2.5 yrs vs 1.6 yrs, and median OS 163 vs 154 months, p=0.53) [12,15]. Based on the results of the studies to date, cytoreduction seems to prolong disease progression and may improve survival in patients with metastatic small bowel and pancreatic NETs. Therefore, the decision to adopt a 90% vs 70% debulking threshold should not be determined by the site of the primary tumor until further data show otherwise. Removal of an asymptomatic primary tumor in the metastatic setting is still controversial since the benefit is exclusively to improve PFS; there is no clear evidence of improved OS. Therefore, with current limited data, there are many factors to be considered before attempting surgical removal of the primary tumor, whether it is for improving symptoms in functional tumors or to avoid bowel obstruction in small bowel NETs. Ultimately, the operability of these patients should be determined by a multidisciplinary team to ensure that benefits outweigh the risks associated with postsurgical morbidity.

Does Grade Affect Cytoreduction Threshold?

Tumor grade is an important factor that impacts prognosis and predicts surgical outcome in GEP-NETs; grade determined by Ki-67 index is strongly associated with both OS and PFS [19,20]. For the patients undergoing cytoreduction, lower tumor grades (Grades 1/2) were associated with survival improvement compared to higher grade tumors (G3), in both small bowel and pancreatic NETs [15,16]. Benefits of cytoreduction in lower grade tumors were documented in the liver cytoreduction thresholds of ≥ 90% and 70%. Bertani, et al. showed improved 5-yr OS in patients with G1 and G2 small bowel NETs who had ≥ 90 liver cytoreduction (90.8% and 76.4%, p=0.012) [16]. For patients who had 70% liver debulking, Scott et al. reported a median OS of 163 months in small bowel NETs and 154 months in pancreatic NETs with G1/G2 tumors [15]. In contrast, patients with high grade (G3) tumors had significantly lower survival (5-yrs OS 0%) suggesting minimal to no benefit from debulking surgery in this subgroup of patients. There is no evidence that lowest grade (G1) has better outcome with cytoreduction compared to intermediate grade (G2). One study by Graff-Baker et al. found that G2 did not correlate with either liver progression-free survival (p=0.10) or disease-specific survival

(p=0.06) compared to G1 tumors in patients who had 90% liver cytoreduction [10]. Therefore, both liver cytoreduction thresholds can be considered for both G1 and G2 GEP-NETs. Higher grade tumors (G3) are more aggressive with higher risk of recurrence, and more data are warranted before considering cytoreduction in this subgroup of patients. This is particularly important since many of the studies reviewed antedate the distinction between G3 NET and poorly differentiated neuroendocrine carcinomas.

Are There Significant Differences in Post-Operative Complications and Carcinoid Crisis Between Both Cytoreduction Thresholds?

Eight of the twelve studies reviewed reported post-operative complications [4,5,7-9,12,15,17]. In these studies, 14-49% of the patients in the 90% cytoreduction group and 22-64% in the 70% group had post-operative complications. Only one study actually compared 90 to 70% cytoreduction and showed no difference in post-operative complications (49% vs 48%, p 0.29) [15]. The most reported complications were intra-abdominal abscess, wound infection and biliary leak. However, the 30-day mortality rate for patients with ≥ 90% cytoreduction was between 1.1-2.7% and 0% in those with 70% cytoreduction; none of the studies compared the two thresholds directly. Ultimately, the data presented were even more limited for the incidence of carcinoid crisis and none of the studies compared the two thresholds accordingly.

Conclusion

Compared to many other cancers, the presence of metastatic disease in GEP-NETs does not preclude surgical treatment and, in fact, surgical debulking of hepatic metastases has been associated with improved symptoms, quality of life, and survival in the metastatic setting. In this systematic review, the current literature regarding this issue consists exclusively of retrospective data that discuss the associated benefit of liver debulking surgery in patients with metastatic GEP-NETs. Overall, debulking of liver metastases is associated with improved outcome compared to historical controls. Even though most studies have adopted ≥90% as the cytoreduction threshold, there is limited evidence to restrict cytoreduction to this level since there is no significant difference in outcome once ≥70% cytoreduction can be achieved. This conclusion is supported by several retrospective analyses, including studies conducted by Maxwell, et al., Graff-Baker et al. and the Oregon University group. All these studies argued that the cytoreduction threshold should, in fact, be reduced to the 70% level since there is no significant difference in OS when compared to the ≥90% group. It is critical to note that both cytoreduction groups were associated with a high 5 year recurrence rate (>80%) due to microscopic liver metastases.

Of the many factors that may affect the clinical benefit of liver cytoreduction, only highest grades (G3) and bulky liver tumor burden (≥ 25%) seem to have a negative impact. The summarized data show that patients with lower liver tumor burden defined as < 25% demonstrated significantly improved PFS and OS compared to those with higher tumor burden ≥ 25%. Similarly, patients with high grade (G3) NETs seems to have significantly lower clinical benefit compared to low and intermediate grades, however these data are confounded by the inclusion of tumors that today would be considered neuroendocrine carcinomas rather than G3 neuroendocrine tumors. There was no significant difference in outcome related to the primary site, therefore liver debulking should not be determined by the site of disease origin. In summary, we have identified a consistent outcome benefit in both ≥90% and ≥70% cytoreduction groups, which may support expanding the eligibility criteria for liver debulking to the 70% threshold. Important predictive factors to select patients who are likely to achieve greater benefit from liver cytoreduction include tumor burden and those with lower-intermediate grades (G1/2). Surgical cytoreduction should be highly selective through multidispilinary approach for patients with high liver tumor burden, extrahepatic disease and higher grades (G3). However, there are significant limitations in the retrospective nature of these studies with potential selection bias. Future clinical trials should prospectively compare the benefit among different liver cytoreduction thresholds and with systemic medical treatments in patients with metastatic GEP-NETs.

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