Neoadjuvant on the gastroenteropancreatic neuroendocrine tumors: A Systematic Review and Meta-analysis

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Abstract

Background

Clinical value of neoadjuvant therapy has been proven in many malignancies. With a low prevalence of neuroendocrine tumors, the survival benefits of neoadjuvant therapy in gastroenteropancreatic neuroendocrine tumors (GEP-NET) are still unclear based on the up-to-date literature.

Aim

To assess the effectiveness of neoadjuvant therapy on GEP-NET.

Methods

Articles were searched electrically on PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, ClinicalTrials.gov and China National Knowledge from inception to 30th June 2020. The survival benefit was assessed by Hard ratio (HR) for overall survival (OS). Median OS, progression-free survival (PFS) and complications were also compared.

Results

This meta-analysis eventually included eight studies with a total of 457 patients. The overall survival of GEP-NET patients in the neoadjuvant therapy group was improved significantly (HR = 0.52; 95% confidence interval, 0.41–0.66; $P=0.008$). There was a dramatic improvement in OS (5-year OS 65.25% vs. 46.79% $P<0.001$) and PFS (5-year PFS 30.64% VS 14.46%, $P=0.04$) in the neoadjuvant therapy group. There was no difference in the postoperative complications among the two groups ($P=0.52$).

Conclusions

Patients with operable GEP-NETs can achieve a significant improvement in overall survival with neoadjuvant therapy. Further large randomized clinical trials are expected to confirm the results.

Background

Neuroendocrine tumors (NETs) are a family of heterogeneous tumors arising from neuroendocrine cells. The incidence of neuroendocrine tumors is relatively low (6.98 per 100 000)[1]. Given the increased detection of early-stage disease and stage migration, it is not surprising that its incidence is gradually increasing [1, 2]. Therapeutic options for neuroendocrine tumors are multitudinous, such as chemotherapy, chemoradiotherapy, surgery, somatostatin analogs, and peptide receptor radionuclide

therapy (PRRT). To date, surgical resection remains as the only means to cure GEP-NET. A characteristic feature of neuroendocrine tumors is the presence of metastases, with the liver being the most the dominant site of metastases. Given its limited systemic therapy and relatively indolent nature, metastases were not an absolute surgical contraindication for NET.[3] Cytoreductive surgery has been proved to be associated with better survival outcomes[4] and was recommended for G1 / G2 NETs with resectable liver metastases[5]. Hence, it is crucial to get access to surgery in advanced GEP-NET.

At the same time, despite the clear benefit of surgical resection in relieving symptoms and prolonging survival, the recurrence rate remained high even in patients who obtained complete resection or a mirror-negative incision margin[6]. Neoadjuvant therapy is considered as a multimodal therapy which aims at improving survival and has been broadly investigated[7]. Neoadjuvant therapy prior to surgery can convert unresectable tumors into resectable tumors and reduce recurrence rates by shrinking the tumor size and destroying micrometastatic lesions. The benefits of neoadjuvant therapy have been proven in different digestive system tumors such as gastric cancer, colorectal cancer, pancreatic cancer, and liver cancer [8–10]. But owing to its relative rarity, there is a lack of uniform knowledge about the effect of neoadjuvant therapy on GEP-NETs. Therefore, we performed this review to evaluate the effectiveness of neoadjuvant treatment in patients with GEP-NETs. The primary endpoint was the overall survival (OS) and the secondary endpoint was the rate of complications.

Methods

In accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-Analysis of Observational Studies in Epidemiology[11, 12], we performed this systematic review and meta-analysis which has been registered at the International Prospective Register of Systematic Reviews(number CRD42020207903)

1. Search strategy and inclusion criteria

The search was formulated in PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, ClinicalTrials.gov, and China National Knowledge Infrastructure using the same subject headings and keywords. Search terms included (neuroendocrine tumor OR neuroendocrine neoplasm OR neuroendocrine carcinoma OR mixed neuroendocrine-non-neuroendocrine neoplasm OR mixed adenoneuroendocrine carcinoma OR carcinoid) AND (neoadjuvant OR preoperative) AND (gastrointestinal OR gastroenteropancreatic OR digestive OR gut OR pancreas).

2. Data extraction

Two authors (Chen and Zhu) independently extracted information from eligible studies using standardized forms. Baseline clinical characteristics (author, year, country, and study design, included number, age, genders), endpoint-related variables (HR for OS and PFS, 3-Year OS,5-Year OS, 3-Year PFS,5-Year PFS), complications, and pre- and post-operative TNM grades were extracted. All discrepancies between the reviewers were resolved by consulting a third reviewer.

3. Inclusion Criteria and Exclusion Criteria

The inclusion criteria for clinical articles were (1) being a definitive pathologic diagnosis of GEP-NETs, (2) patients without metastases or with only liver metastases having undergone surgery and at least one preoperative neoadjuvant therapy (including chemotherapy, radiation therapy, chemoradiotherapy and PRRT therapy), (3) at least including one of HR or survival rate, and (4) having full text of studies available.

The exclusion criteria were (1) diagnoses not confirmed by pathology, (2) only endoscopic treatment, (3) originating outside the digestive system and metastasizing to the digestive tract, (4) cancers with neuroendocrine differentiation, (5) intraoperative chemotherapy, and (6) fewer than ten patients included.

4. Quality assessment

Two reviewers independently assessed the eligibility and validity of each study via the Cochrane tool for assessing the risk of bias in randomized controlled trials (RCTs) and the Newcastle-Ottawa scale in observational studies. Newcastle-Ottawa scale measured quality in the three parameters of selection, comparability, and exposure/outcome as well as allocated a maximum of 4, 2, and 3 points respectively. High-quality studies scored greater than 7, moderate-quality studies scored between 5 and 7, and low-quality studies scored under 5. We conducted research bias detection on the articles included. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method serves as the guideline in the systematic review and meta-analysis. Each study was independently assessed by 2 authors, and any disagreement was to be discussed with a third reviewer and resolved in consensus.

5. Statistical Analysis

This study primarily focused on the evaluation of the overall survival time, meanwhile covering the analysis of complications, PFS, 5-year OS and 5-year PFS.

For articles that presented Kaplan-Meier curves without Hazard Ratio or related survival information, we used software *Engauge Digitizer* (version 12.0) and *SPSS* (version 21) to extract variables in the coordinates of the Kaplan-Meier curves. Cochrane I^2 and χ^2 statistics were applied to estimate statistical heterogeneity, $P < 0.05$ and $I^2 > 50\%$ being highly heterogeneous. Random-effects models were conducted in the case of $I^2 > 50\%$; otherwise, fixed-effects models were chosen. Statistical significance was defined at the level of 5% ($P = 0.05$). The Inverse variance method was employed in analyzing subgroups. Odds ratios (OR) were calculated for the analysis of complications. *Egger* linear regression was conducted to define publication bias. All statistical analysis was performed in the software *STATA* version 14.0 and *RevMan* (version 5.3).

Results

1. Study Selection and Risk of Bias Assessment

We identified 889 records from six databases (*Figure 1*). After removing duplicates, 841 publications were screened based on the title and the abstract, and 115 of them were selected for full-text review. Finally, 8 articles involving 457 participants were included (*Table 1*). All of them were retrospective studies. According to the overall Newcastle-Ottawa Scale, the overall research quality was moderate (range, 5-8, mean 6.5, *Table 2*). Among the 8 studies, five studies adopted adjuvant chemotherapy [13-17], one study chose PRRT[18], and two studies had PRRT combined with chemoradiotherapy[19, 20]. In the studies involving chemotherapy, platinum-based regimens were the most common, with etoposide/cisplatin regimen accounting for the highest proportion.

There were no significant differences between the two groups in the baseline characteristics: age($P=0.64$), gender($P=0.07$), percentage of clinical TNM($P=0.63$), percentage of clinical T classification($P=0.23$), and clinical N classification($P=0.46$). Significant heterogeneity ($I^2=37.2\%$) was not present. Evaluation of publication bias basing on overall survival (OS) was examined with *Egger's* test ($P=0.462$) which indicated a low heterogeneity of the included literature and no significant publication bias (*Supplement figure 1*).

2. Survival Analysis

There was a drastic improvement in overall survival in the neoadjuvant group against the surgery-alone group (5-year OS 65.25% vs. 46.79% $P<0.001$, *Figure 2*; 3-year OS 75.66% vs. 63.5% $P<0.001$, *Figure 3*; and 1-year OS 93.42% vs. 82.48% $P=0.001$). The pooled risk ratio values after the combined analysis were 0.92, 0.81, and 0.68 for 1,3,5-year respectively.

The pooled PFS similarly favored neoadjuvant therapy. The PFS for 3 years and 5 years were 45.2% and 30.64% in the neoadjuvant group, higher than that of 27.96% ($P=0.04$) and 14.46% ($P=0.04$) in the surgery-alone group respectively.

As shown in *Figure 4*, the pooled HR was 0.52(95% CI: 0.41-0.66), suggesting the benefit from neoadjuvant therapy ($I^2=36\%$, $P<0.001$). In the subgroup analysis of NETs with liver-only metastases, the pooled HR had a result of 0.62(95% CI: [0.41, 0.94]) with $I^2=23\%$.

Reconstructed *Kaplan–Meier* survival curves for overall survival had a HR of 0.86(95%CI, 0.51– 0.91, $P=0.008$). Neoadjuvant groups with a median OS of 71.05 months exhibited a prolonged survival compared to surgery-alone group groups (49.6 months, 95% CI,189-237, $P<0.001$) (*Figure 5*). Depending on the tumor site, we performed another subgroup analysis, which showed that the pooled HR of pancreatic NETs was 0.49 95% CI (0.38- 0.65), $I^2=37\%$, $P<0.001$.

3. Complications and postoperative pathology

There was no significant difference in postoperative complications between the two groups (30% vs 29.4%, $P=0.52$). The rate of R0 resection in the neoadjuvant group was slightly but not significantly higher than that of the surgery-alone group($P=0.28$). This may be related to the fact that most articles do not

mention the R0 resection rate. In view of pathological findings, the maximum diameters of resected tumors were smaller in the neoadjuvant group than in the surgery-alone group (4.4 ± 2.1 cm vs. 5.7 ± 2.8 cm, $P = 0.02$). Furthermore, the rate of post-operative N0 was higher in the neoadjuvant group (68.1% vs. 49.09%, $P=0.02$). However, the difference in postoperative pathological TNM grading was not statistically significant($P=0.13$).

Discussion

There has been a gradual growth in the incidence of NETs in recent years but no significant change in the survival of patients with high-grade NET[16, 21]. This situation may reflect a lack of awareness in the treatment. Given the biological similarities, the main treatment of NET was extrapolated from the experience in small-cell lung cancer (SCLC) currently[14, 16, 22]. Neoadjuvant therapy in SCLC has been proved effective in some studies [23–25]. In digestive system tumors such as gastric cancer, colorectal cancer, and pancreatic cancer, neoadjuvant chemotherapy can improve the OS or PFS and manifests its efficacy and safety[26]. Effective neoadjuvant therapy can improve the potential respectability by downstaging the disease and addressing the micrometastatic lesions through cytotoxic effects[27]. Previous studies had shown that the statistical cure for neuroendocrine liver metastasis tumors (NELM) with liver resection was possible[28]. Hence, we included neoadjuvant studies on patients with only liver metastases. However, due to limited studies, whether neoadjuvant therapy confers a survival benefit in GEP-NET still lacks sufficient clinical data. Therefore, we performed this meta-analysis.

In the current study, we found that the pooled HR for OS in the neoadjuvant chemotherapy group was 0.52 [95% CI, 0.41–0.66], suggesting a nearly 48% reduction in the risk of death in the neoadjuvant chemotherapy group compared to the surgery-alone group. There was no publication bias among the included trials. In respect of OS, neoadjuvant therapy had a better 5-year overall survival rate or progression-free survival rate, with the 5-year survival time up to 63.83%. The reconstructed Kaplan-Meier on median OS showed a longer overall survival in the neoadjuvant without increasing postoperative complications, demonstrating that neoadjuvant therapy is a safe and effective treatment.

Platinum-based chemotherapy is recommended as the first-line therapy for advanced NET[29]. In this meta-analysis, platinum-based chemotherapy (such as etoposide/cisplatin regimen, irinotecan/cisplatin regimen) was the most common preoperative regimen. Our study included not only neoadjuvant chemotherapy but also neoadjuvant PRRT, a targeted SSTR2 receptor-based regimen that has a definite anti-tumor effect by causing deleterious DNA damage on tumor cells via radionuclides[30]. Due to the small number of studies, we could not compare the benefits of neoadjuvant chemotherapy and neoadjuvant PRRT therapy.

This study confirmed the survival benefit of neoadjuvant therapy, possibly primarily through a reduction in tumor diameter and lymph node metastasis rate. Larger tumor size has been proven to be associated with a poor tumor prognosis. Our analysis identified a smaller diameter in the postoperative specimens of the neoadjuvant group, suggesting that neoadjuvant therapy may be clinically beneficial by downsizing

tumor sizes. However, due to the missing data related to preoperative tumor diameter, further studies are expected to confirm this hypothesis. Lymph node metastasis was an independent risk factor for poor prognosis in NETs[31, 32]. Our study showed that there was no difference in clinical N stage between the two groups before operation ($P = 0.46$). That the neoadjuvant group had a higher pathological N0 lymph node ratio after the operation suggests that neoadjuvant therapy achieves better survival rates by reducing metastasis of lymph nodes.

Traditionally, neoplasm metastasis is a relative contraindication to surgery, whereas the majority of patients with advanced GEP-NETs have liver metastases. Surgical resection is still an option in the absence of diffuse involvement, compromised liver function, or extrahepatic metastases[33–35] and the clinical value of hepatic resection in NETs with only liver metastases has been confirmed[36–38]. Our neoadjuvant study suggested that the pooled HR was 0.62 95% CI (0.41–0.94) for patients with NELM, illustrating that patients with NELM can achieve further clinical benefits from neoadjuvant therapy. Molecularly targeted therapy such as *Everolimus* or inhibitors of *VEGFR* are also systemic treatment options for GEP-NETs, but the studies on their role in neoadjuvant therapy were few and more research is needed.

Our study also had some shortcomings. Firstly, the use of meta-analysis for observational studies is controversial and the heterogeneity of study design, disease characteristics and patient population may affect the aggregated results. However, because of the low overall prevalence, there are no high-quality large RCTs to study follow-up. Secondly, all included studies were retrospective, so there was a potential imbalance in patient characteristics, and some of the studies did not take neoadjuvant as the main observation point, leading to missing data in the preoperative tumor diameter, specific preoperative chemotherapy regimens and frequency, types of NETs(functioning and non-functioning) and/or location of NETs, all of which expect more in-depth studies. Although our analysis indicated that survival was affected by neoadjuvant, we need more well-designed randomized controlled studies to control bias such as tumor grade, localization, and pathological classification. And these studies need to focus more on the reasonable number of neoadjuvant therapies and reasonable operation time.

However, this is the first systematic analysis attempting to assess the most appropriate treatment for advanced NETs. With low overall heterogeneity and significant publication bias, this study improves the feasibility of the results and corroborates the clinical efficacy of neoadjuvant therapy in GEP-NET.

Conclusion

Neoadjuvant therapy can improve the prognosis of GEP-NETs.

Abbreviations

GEP-NET: gastroenteropancreatic neuroendocrine tumors

RCTs: Randomized Controlled Trials

CIs: Confidence Intervals

HR: Hazard Ratio

SCLC: Small-cell lung cancer

NELM: neuroendocrine liver metastasis tumors

PRRT: peptide receptor radionuclide therapy

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication: Not applicable.

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: CHY put forward ideas, analyzed data entry, and wrote articles. ZCX performed data analysis and reviews articles. HXK and DWJ involved in the analysis and interpretation of data. SLM put forward ideas, read and revised the manuscript. All authors have read and approved the manuscript, and ensure that this is the case.

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Tables

Table 1: baseline characteristics

Adult Studies	Study Design	No of patients	Main neoadjuvant types	Outcome
Partelli, S. 2018 Italy	Retrospective, dual-center, 1:1 case-matched comparison Pancreas only	Intervention: 23 No intervention: 23	PRRT ⁹⁰ Y-DOTATOC ¹⁷⁷ Lu-DOTATATE	Kaplan-Meier curves for DFS, PFS. pathologic features
Ma, F. 2020 China	Retrospective, Single-center Stomach only	Intervention: 20 No intervention: 49	Chemotherapy Etoposide/cisplatin Docetaxel, oxaliplatin, and S-1(DOX) S-1/Oxaliplatin (SOX)	HR for OS Kaplan-Meier curves for OS
Cloyd, J. M. 2018 US	A prospectively maintained database Pancreas only	Intervention: 20 No intervention: 49	Chemotherapy Fluorouracil+ doxorubicin + streptozocin	Kaplan-Meier curves for OS, RFS
Xie H 2020 China	the National Cancer Database 1:1 case-matched comparison Pancreas only	Intervention: 38 No intervention: 38	NA	Kaplan-Meier curves for OS, HR for OS
van der Veen, A. 2018 Netherlands	A nationwide cohort study Esophageal and gastric	Intervention: 25 No intervention: 22	Chemotherapy; Chemoradiotherapy Epirubicin + cisplatin + capecitabine Epirubicin + oxaliplatin+ capecitabine Radiotherapy + carboplatin + paclitaxel Radiotherapy + cisplatin+ etoposide	Kaplan-Meier curves for OS
XU L 2017 CHINA	Retrospective, Single-center Esophagus only	Intervention: 16 No intervention: 50	Chemotherapy	1,3,5-year OS, DFS; Kaplan-Meier curves for OS

Alese, O. B. 2019 USA	A National Cancer Database Study Pancreas only	Intervention: 54 No intervention: 20	Chemotherapy Chemotherapy: Cisplatin/etoposide; Carboplatin/etoposide; Temozolomide/capecitabine	HR for OS 3,5-year OS, PFS, Median OS, PFS
Galleberg, R. B. 2017 Norway	Retrospective, dual- center Gastroenteropancreatic			

Table 2: Newcastle-Ottawa scale scores of included studies, with a score of at least 6 indicating high quality.

Author	Selection	Comparability	Exposure
Partelli, S.	3	2	3
Ma, F.	2	2	3
Cloyd, J. M.	2	3	2
Xie, H.	3	3	2
van der Veen, A.	3	2	2
Xu, L.	2	2	1
Alese, O. B.	2	1	1
Galleberg, R. B.	3	1	2

Figures

Figure 1

Flowchart for article screening

Figure 2

The 3-year OS between the neoadjuvant and the surgery alone.

Figure 3

The 5-year OS between the neoadjuvant and the surgery alone.

Figure 4

Pooled HR for total OS

Figure 5

Reconstructed Kaplan–Meier survival curves for overall survival

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