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Review

Neoadjuvant therapy for advanced pancreatic neuroendocrine tumors: an emerging treatment modality?

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ABSTRACT

OBJECTIVE: Complete surgical resection is the only potentially curative treatment of localized pancreatic neuroendocrine tumors. Unfortunately, a significant proportion of these patients present with unresectable locally advanced tumors or massive metastatic disease. Recently, a new therapeutic approach for this subset of patients has emerged consisting of neoadjuvant therapy followed by surgical exploration in responders. DESIGN: We searched MEDLINE for the purpose of identifying reports regarding neoadjuvant treatment modalities for advanced pancreatic neuroendocrine tumors. RESULTS: We identified 12 studies, the vast majority of which were either case reports or small case series. Treatment options included chemotherapy, radiotherapy, peptide receptor radionuclide therapy, biological agents or various combinations of them. CONCLUSIONS: Increasing evidence supports the application of neoadjuvant protocols in advanced pancreatic neuroendocrine tumors aiming at tumor downsizing, thus rendering curative resection feasible. Given that prospective and controlled randomized clinical trials from high-volume institutions are not feasible, expert panel consensus is needed to define the optimal treatment algorithm.

Key words: Locally advanced-liver metastasis, Neoadjuvant therapy, Pancreatic neuroendocrine tumor

INTRODUCTION

Pancreatic neuroendocrine tumors (pNETs) are uncommon neoplasms that represent 1-2% of all pancreatic neoplasms.[1] The World Health Organization (WHO) classification of 2010 adopted the European Neuroendocrine Tumor Society (ENETS) grading system, categorizing NETs as NET G1 (low grade), NET G2 (intermediate grade) and poorly differentiated neuroendocrine carcinomas (NECs).[2,3] A substantial percentage of pNETs (65-80%) is associated with malignant behavior and recurrence following resection. However, in many cases disease progression may be very slow resulting in prolonged survival.[1] pNETs are currently staged according to the American Joint Committee on Cancer (AJCC) classification of 2010 (7th edition).[4]

Complete surgical resection (R0 excision) is the only potentially curative treatment of localized pNETs.

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While an aggressive surgical approach has been advocated,[5] surgical debulking or planned R2 resection have not received wide support.[6]

Unfortunately, a significant proportion of patients with pNETs present with unresectable locally advanced tumors or massive metastatic disease, which render surgical treatment unfeasible.[7,8]

Recently, a new therapeutic approach for this subset of patients with inoperable pNETs has emerged consisting of induction therapy in the neoadjuvant setting followed by surgical exploration in responders. Neoadjuvant chemotherapy has been extensively used for locally advanced adenocarcinomas with remarkable clinical results over the last few decades. With regard to pNETs, this approach is occasionally considered and suggested by several authors, mainly through case reports or small case series.

The purpose of this review is to update current knowledge regarding neoadjuvant treatment of locally advanced pNETs. We carried out a comprehensive search of the literature, using PubMed (http://www.ncbi.nlm.nih.gov/pubmed). The following keywords were used in the search: pancreatic neuroendocrine tumors, locally advanced, neoadjuvant therapy, preoperative chemotherapy, preoperative radiotherapy. No language restrictions were applied. The PubMed search was extended up to April 2015 to retrieve the latest additional publications. Moreover, the bibliographies of reviewed articles were scrutinized to obtain any other references that eluded the primary search. Original research articles [randomized controlled trials (RCTs), prospective and retrospective studies], meta-analyses, reviews, editorials, commentaries, case reports, case series and letters were included.

DEFINITIONS OF LOCALLY ADVANCED PANCREATIC TUMORS

Locally advanced pancreatic cancers are defined as tumors adherent to or invading adjacent structures, including celiac and superior mesenteric vasculature (T4 or stage III disease). Recently, two distinct subgroups of such tumors have been identified: borderline resectable and locally advanced unresectable pancreatic tumors.[9]

According to the consensus-based guidelines from the National Comprehensive Cancer Network (NCCN),[10] criteria for unresectability are as follows:

- For pancreatic head and body tumors: greater than 180 degrees superior mesenteric artery (SMA) encasement or any celiac artery abutment, unreconstructable superior mesenteric vein (SMV)/portal vein (PV) occlusion, aortic invasion or encasement.
- For pancreatic tail tumors: greater than 180 degrees SMA encasement or any celiac artery abutment.
- For all sites: distant metastases, metastases to lymph nodes beyond the field of resection.

The definition of borderline resectable tumors is variable, mainly due to differences between centers in feasibility of SMV reconstruction. However, the most commonly cited criteria are those recommended by a consensus statement of the American Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract, which have also been included in the guidelines of the NCCN.[10,11] According to this definition, borderline resectable pancreatic tumors present the following characteristics:

- No distant metastases.
- Venous involvement of the SMV/PV demonstrating tumor abutment with or without impingement and narrowing of the lumen, encasement of the SMV/PV but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement, but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction.
- Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct tumor abutment of the hepatic artery, without extension to the celiac axis.
- Tumor abutment of the SMA not to exceed >180 degrees of the circumference of the vessel wall.

Concerning neuroendocrine tumors, the ENETS has set up a tumor-node-metastasis (TNM) staging system as well as a grading system (G1, G2, and G3) (Table 1).[3]

Table 1. Grading proposal for foregut neuroendocrine tumors from ENETS[5]

Grade	Mitotic count (10 HPF)[a]	Ki-67 index (%)[b]
G1	<2	≤2
G2	2-20	3-20
G3	>20	>20

[a]10 HPF: high power field=2 mm^2, at least 40 fields (at 40 × magnification) evaluated in areas of highest mitotic density; [b]MIB1 antibody; % of 2,000 tumor cells in areas of highest nuclear labeling.

In addition, the AJCC has proposed a TNM staging classification significantly different to the ENETS staging system.[4] From the surgical point of view, the AJCC staging system incorporates in T4 tumor assessment the importance of anatomical correlation of the tumor with the adjacent vascular structures, which is the cornerstone of resectability in pancreatic neuroendocrine tumors. Of note, the ENETS tumor staging system, which equates tumor infiltration of viscera with major vascular involvement, is not compatible with current clinical practice. It should be stressed that preoperative imaging studies showing possible vascular involvement as well as definite detection of this intraoperatively are usually considered contraindications to surgery.

Aggressive surgery for T4 tumors including superior mesenteric vein reconstruction can be contemplated, but the surgical risk-benefit ratio should be carefully weighed.[12,13]

Oncologic perspectives

Nowadays, the use of neoadjuvant therapy is an established treatment in patients with pancreatic ductal adenocarcinoma (PDAC). PDAC carries the worst prognosis of all malignancies of the alimentary tract. Despite recent advances in imaging studies, only 10 to 20% of patients have resectable disease at the time of presentation. Of the remaining patients, 30 to 40% present with locally advanced tumors. Median survival for these patients is 8-12 months.[9]

Due to their poor prognosis, such patients are candidates for neoadjuvant therapy with the aim of tumor downsizing (or even disease downstaging) and subsequent resection. Moreover, neoadjuvant therapy is better tolerated by patients and allows for the identification of those patients with rapid disease progression despite therapy who are not expected to benefit from surgery.

Two meta-analyses including series of patients with pancreatic adenocarcinoma have concluded that approximately one third of patients with locally advanced, unresectable or borderline resectable tumors can be resected after neoadjuvant therapy, with survival rates comparable to those of patients with initially resectable tumors.[14,15] Therapeutic options include chemotherapy, chemoradiotherapy or a combined approach. Radiotherapy alone has been tried to a lesser extent. However, the optimal regimen in this setting is not to date established.[9]

The role of neoadjuvant therapy in the treatment of advanced pNETs

In regard to neuroendocrine pancreatic tumors, either synchronous or metachronous resection of the primary and metastatic tumors is recommended to be performed whenever possible.[12,16,17]

Even in the setting of locally advanced tumor and/or metastatic disease, surgery may be the treatment of choice aiming at tumor reduction and palliation of mass effect or hormone-related symptoms.[18] Surgical excision should be performed only if more than 90% of the tumor mass can be resected.[19] On the other hand, it has been suggested that palliative debulking surgery has no significant effect on survival as compared to palliation without surgery.[20]

Regarding inoperable pNETs, the current guidelines suggest observation for patients with pNETs G1/G2 who are asymptomatic, with low tumor burden and stable disease. In the case of symptomatic patients with large tumor volume or progressive disease, first-line therapy recommendations include biological agents (sunitinib, everolimus), chemotherapy, arterial embolization, chemoembolization, ablative therapy, cytoreductive surgery, supportive medical care and somatostatin analogs. Patients with inoperable pancreatic NECs should be started on cisplatin- or etoposide-based chemotherapy or offered the chance to participate in clinical trials.[18]

During the last decade, several institutions have reported response rates of 39% to 71% with non-surgical treatments in patients with advanced pNETs,[21] although the majority of these published studies are

single-arm, non-randomized ones with a small number of patients and therefore do not report clinically meaningful outcomes.[22] Nevertheless, a subgroup of these patients with initially inoperable tumors turned out to be resectable as a result of significant downsizing caused by systemic therapy. This fact along with the substantial recurrence rates reported after surgical approaches point to the benefit of neoadjuvant concepts in patients with advanced pNETs.[7,21]

Helical CT with 3-dimensional reconstruction and magnetic resonance visceral angiogram are used to assess resectability of pancreatic tumors following neoadjuvant chemotherapy. A recent large series of patients who presented with inoperable or borderline resectable pancreatic adenocarcinoma and received neoadjuvant folfirinox with or without chemo-radiotherapy demonstrated impressive improvements.[23]

The well documented result of the study shows that traditional imaging criteria for resectability following neo-adjuvant therapy were not accurate and the authors suggested serial intraoperative biopsies around the involved vascular structures before attempting resection. In the field of neuroendocrine pancreatic tumors, Norton et al demonstrated that radiological abutment or even possible vascular involvement is not frequently synonymous with vascular involvement at surgery.[12]

The potential role of induction therapy in advanced pNETs has been assessed only in a limited number of studies (Table 2), of which the vast majority are case reports. In other retrospective studies which have included larger series of patients, the therapeutic regimen was not given initially in the neoadjuvant setting. Surgical exploration following therapy was undertaken in only a few selected patients that presented the best response. Therapeutic options that have been studied include chemotherapy, peptide receptor radionuclide therapy (PRRT), biological agents and radiotherapy.

Much controversy exists over the appropriate term that should be used to describe the effect of neoadjuvant treatment on disease. Although most authors use terms such as: tumor downsizing, reduction, shrinkage or partial response. There have also been reports employing the term: disease downstaging. Such publications should be judged cautiously because in some of them the term has proven to have been used inappropriately.[24] Moreover, the primary goal of neoadjuvant therapy should not be disease downstaging, but tumor downsizing in order to render it operable.

CHEMOTHERAPY

Until lately, neuroendocrine tumors have not usually been considered the ideal target for traditional DNA-damaging cytotoxic agents.[18] Sorbye et al first reported in 2007 a patient with pancreatic NEC with liver metastases who responded partially to induction chemotherapy with etoposide plus cisplatin and underwent complete resection. Interestingly, no primary tumor was found in the pancreatectomy specimen. The patient received adjuvant therapy and was alive and free of disease 5 years after the operation.[25]

Lessing et al in 2001 described 3 patients with extrapancreatic NECs who received neoadjuvant therapy with etoposide plus cisplatin. The first patient presented partial response and underwent complete resection. Eighteen months postoperatively the patient is alive and free of disease. The second patient also underwent complete resection after presenting partial response, but died 5 months postoperatively with local recurrence. Complete response was noted in the third patient and no mass was found in surgical exploration. However, the patient had local recurrence one year after the operation.[26]

Sato et al reported a patient with pNET and multiple liver metastases that were treated with S-1, an oral fluorinated pyrimidine which contains tegafur, a prodrug of 5-FU, 5-chloro-2,4-dihydroxypyridine and potassium oxonate. The primary tumor presented partial response, while liver metastases presented complete response, allowing complete resection. The patient was alive and free of disease 6 months after the operation.[27] It must be stressed that this is the only report of disease downstaging after neoadjuvant treatment, since, according to the authors, there was complete disappearance of liver metastases.

A very recent retrospective study by Dumont et al included 42 patients with locally advanced pNETs G1/G2 and segmental portal hypertension who were treated with different chemotherapeutic regimens containing 5-FU, streptozocin, doxorubicin, cisplatin,

Table 2. Studies reporting neoadjuvant treatment of advanced NETs

	Author, year	No of pts[¥]	Disease characteristics	Induction therapy	Comments	Follow-up
1	Sorbye et al, 2007[25]	1	Pancreatic NEC, liver metastasis	Etoposide plus cisplatin	Partial response. R0 resection, no primary tumor found in pancreatectomy specimen	Adjuvant therapy 5 years - free of disease
2	Kwekkeboom et al, 2008[30]	4/310	Non-functioning pNETs	PRRT (^{177}Lu-octreotate)	Partial response. R0 resection. One died postoperatively from complications	nr
3	Kaemmerer et al, 2009[24]	1	Pancreatic NEC	PRRT (^{90}Y-DOTA-TATE)	Partial response. R0 resection	18 months - free of disease
4	Stoeltzing et al, 2010[31]	1	Resected pNET, bilobular liver metastases	PRRT (^{90}Y-DOTA-TOC)	Partial response. R0 resection of liver metastases	12 months - free of disease
5	Sato et al, 2010[27]	1	pNET, multiple liver metastases	S-1	Partial response (primary tumor)- complete response (liver metastases). R0 resection.	6 months - free of disease
6	Sowa-Staszczak et al, 2011[33]	2/6	pNETs, 1 with liver metastases	PRRT (^{90}Y-DOTA-TATE)	Partial response (primary tumor). R2 resection Partial response (primary tumor) - complete response (liver metastases). R0 resection	nr
7	Lessing et al, 2011[26]	3	NECs (2 duodenum, 1 rectosigmoid)	Etoposide, cisplatin	Partial response. R0 resection Partial response. R0 resection Complete response. No tumor at exploration	18 months – free of disease 5 months – recurrence/death 12 months – recurrence
8	Devata et al, 2012[29]	1	pNET	Capecitabine plus temozolomide	Partial response. R0 resection	3 months - free of disease
9	Barber et al, 2012[34]	1/5	pNET	PRCRT (^{177}Lu-octreotate plus 5-FU)	Partial response. R0 resection	12 months – free of disease
10	Lee et al, 2013[35]	1/9	pNET	RT	Partial response. R0 resection	5 years – free of disease
11	Dumont et al, 2015[28]	28/42	pNETs G1/2 with segmental portal hypertension	Chemotherapy (5-FU, streptozocin, doxorubicin, cisplatin, etoposide, oxaliplatine)	No radiological improvement in SPH signs. 13 R0, 6 R1 and 9R2 resections. Incomplete resections due to metastatic disease. All primary tumors resected	5-year overall survival [R0] vs [R1/R2/no resection]: 78% vs 55% (p=0.227)
12	Ezzidin et al, 2012[32]	1	pNET with liver metastases	PRRT (^{177}Lu-octreotate)	Partial response. R0 resection, almost complete regression of liver metastases	22 months – complete local remission

NECs: neuroendocrine carcinoma(s); pNETs: pancreatic neuroendocrine tumor(s); PRRT: peptide receptor radionuclide therapy; PRCRT: peptide receptor chemoradionuclide therapy; nr: not reported; RT: radiotherapy.

[¥]Patients that underwent surgical exploration following neoadjuvant therapy/patients included in the study.

etoposide and oxaliplatine. No radiological improvement was recorded in segmental portal hypertension signs. Subsequently, 28 of them underwent surgical exploration. Complete resection (R0) was achieved in 13 cases. In 6 patients there was microscopic residual disease (R1 resection) and in the remaining 9 patients there was gross residual disease (R2 resection). It should be underlined that all primary tumors were successfully resected and that incomplete resections were due to intraoperatively found unresectable liver metastases. In survival analysis, a trend towards improved 5-year survival was observed among patients with R0 resections as compared to those with R1/R2 resections and no resection, without yet, reaching statistical significance (78% vs 55% respectively, p=0.227).[28]

BIOLOGICAL AGENTS

Devata et al reported one patient with pNET who responded partially to the combination of two biological agents, capecitabine plus temozolomide, and underwent R0 resection. The patient remained alive and free of disease 3 months postoperatively.[29]

PEPTIDE RECEPTOR RADIONUCLIDE THERAPY

Six studies have reported successful use of peptide receptor radionuclide therapy in the neoadjuvant setting. Kwekkeboom et al retrospectively studied 310 patients with pNETs who received PRRT with ^{177}Lu-octreotate. Four of them, with non-functioning pNETs that responded partially, underwent R0 resection. One of them died postoperatively from surgical complications.[30]

Kaemmerer et al reported a patient with PNEC who responded partially to PRRT with ^{90}Y-DOTA-TATE and was subsequently completely resected. The patient was alive and free of disease 18 months after the operation.[24]

Stoeltzing et al reported another patient with resected pNET and bilobular liver metastases which were successfully resected after partial response to PRRT with ^{90}Y-DOTA-TOC. The patient was alive and free of disease 12 months after the operation.[31]

Ezzidin et al reported a patient with pNET and liver metastases who received neoadjuvant therapy with ^{177}Lu-octreotate demonstrating partial response with tumor shrinkage and one small residual metastatic liver lesion. The primary tumor was then completely resected and the patient remained in complete local remission 22 months after the operation.[32]

In another study, six patients with advanced pNETs were treated with ^{90}Y-DOTA-TATE, two of which underwent surgical exploration following therapy. In one patient the tumor was found to have remained unresectable and an R2 resection was undertaken. In the other one complete response of liver metastases was noted, while the primary tumor was completely resected.[33] Barber et al reported treating five patients with inoperable NETs with the combination of PRRT (^{177}Lu-octreotate) plus 5-FU. One of them underwent subsequent R0 resection and remained 12 months postoperatively alive and free of disease.[34]

RADIOTHERAPY

The use of radiotherapy alone in the neoadjuvant setting in advanced pNETs has been described once by Lee et al. Among nine patients who received external beam radiation, only one was offered surgical resection following radiotherapy. Surgical margins were negative and the patient survived 5 years free of disease.[35]

CONCLUSIONS

Increasing evidence supports the application of neoadjuvant protocols in advanced pNETs. Patients with pNETs are frequently diagnosed with advanced stage disease and inoperable tumors. Provided that an aggressive surgical approach is indicated in patients with pNETs, efforts to downsize locally advanced tumors and make them resectable seem perfectly reasonable.

Several preoperative therapies have been suggested in the literature, including chemotherapy, radiotherapy, biological agents, peptide receptor radionuclide therapy or various combinations of them.

Neuroendocrine tumors are relatively rare tumors, with most of the available evidence deriving from case reports or small case series treating heterogenous

tumors. The latter is due to the fact that prospective and controlled randomized clinical trials from high-volume institutions are not feasible. Expert panel consensus based on the experience of surgeons and endocrinologists who deal with locally advanced pancreatic neuroendocrine tumors, is needed to assess the efficacy and survival benefit of the aforementioned neoadjuvant treatments and define the optimal treatment algorithm. Treatment recommendation for pNETs may not strictly follow the current guidelines and must include individualization and optimization of management.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest and that they received no specific funding for this article.

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