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CASE MANAGEMENT AND CLINICAL CONSEQUENCES

Staged surgery with neoadjuvant ^{90}Y-DOTATOC therapy for down-sizing synchronous bilobular hepatic metastases from a neuroendocrine pancreatic tumor

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Abstract
Purpose Treatment with DOTA-*d*-Phe(1)-Tyr(3)-octreotide (DOTATOC), labeled with beta-emitting radioisotope yttrium-90 (^{90}Y-DOTATOC), has successfully been used for the palliative treatment of patients with advanced somatostatin receptor-expressing neuroendocrine tumors (NETs). However, controversy persists as to whether patients with metastatic NETs of the pancreas should undergo radical (salvage) surgery or receive palliative therapy. We proposed that ^{90}Y-DOTATOC could be used in a neoadjuvant intention for improving therapy of hepatic NET metastases.

Materials and methods We investigated a novel therapy concept in a 49-year-old patient presenting with a neuroendocrine tumor of the pancreatic tail and synchronous multiple bilobular hepatic metastases. After surgical removal of the large primary tumor by extended left en bloc resection of the pancreatic tail, the patient received neoadjuvant ^{90}Y-DOTATOC for therapy of primarily non-resectable bilobular hepatic metastases.
Results The ^{90}Y-DOTATOC therapy resulted in an impressive regression of hepatic lesions, thus facilitating surgical removal of all remaining liver metastases in a second operation (staged surgery). In addition, one lesion was ablated using radiofrequency ablation (RFA). At 1-year of follow-up after hepatic R0 resection/RFA, there was no evidence of tumor recurrence or extrahepatic metastasis.
Conclusions The neoadjuvant use of ^{90}Y-DOTATOC therapy could prove valuable for treatment of advanced pancreatic NETs metastatic to the liver in terms of facilitating R0 resection by applying staged surgery concepts.

Keywords Liver resection · Neoadjuvant therapy · NET · Pancreas · Staged surgery

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Introduction

Although neuroendocrine tumors (NETs) of the pancreas represent an uncommon tumor entity, which account for 2–4% of clinically detected pancreatic tumors, the therapeutic management of advanced or metastatic NETs remains a great challenge [1]. In general, NET of the pancreas may present as single, or multiple, either benign or malignant

lesions that also can be associated with the multiple endocrine neoplasia type 1 syndrome [2]. In addition, these tumors are being categorized based on their functionality into non-functional and functional neuroendocrine lesions, though non-functional tumors may also be "active" by immunohistochemical analysis. However, as suggested by Madura and colleagues [3], the most commonly used definition is that nonfunctioning islet tumors are pancreatic neoplasms with endocrine differentiation that are not associated with a clinical syndrome of hormone hyperfunction. Importantly, in contrast to small benign NETs (i.e., insulinomas) that can easily be resected by standard surgical approaches, advanced nonfunctional NETs have a much less favorable prognosis and demand multidisciplinary oncologic strategies [4]. The predominant clinical issues of malignant NETs comprise early tumor recurrence and metastasis, and the fact that, at diagnosis, about 60% of non-functioning endocrine pancreatic tumors and 50% of gastrinomas are already metastatic [5–7]. The poor prognosis of patients with advanced NETs is clearly reflected by studies on a historic patient population where untreated liver metastases showed a 5-year survival of only 20–30% [7].

Regarding NETs of the pancreas, chemotherapy and radiation therapy have not demonstrated significant antitumoral effects, and, controversially, either a palliative therapy or an aggressive surgical approach have been advocated [8–12]. Moreover, some studies demonstrated that significant differences in median survival and 2-year survival exist between node-positive/node-negative patients and those with metastasis to the liver. Therefore, it has been proposed that patients with localized non-metastatic disease should be considered for a radical pancreatic resection. In contrast, in the presence of synchronous or metachronous hepatic metastases, the treatment strategies are not standardized and less well-defined. The surgical approaches for therapy of advanced and metastatic (liver) NETs of the pancreas comprise cytoreductive therapy, salvage resection, extended liver resections, and even liver transplantation [6, 7, 9, 11, 12]. Interestingly, simultaneous resection of both the primary tumor and all the hepatic metastases did not seem to be an unfavorable prognostic factor in these studies. Nevertheless, surgical resection of liver metastases is feasible in only less than 20% of patients, due to the high percentage of multifocal and bilateral metastases. and the 5-year actuarial survival rate is 73%, with a high probability of recurrence and time to progression that is proportional to the intrahepatic spread.

Recently, a therapeutic approach using DOTA-*d*-Phe(1)-Tyr(3)-octreotide (DOTATOC) labeled with beta-emitting radioisotope yttrium-90 (^{90}Y-DOTATOC) has proven promising efficacy in the (palliative) treatment of metastatic somatostatin receptor (SST-R)-expressing NETs [13, 14]. In clinical trials, ^{90}Y-DOTATOC therapy resulted in either a disease stabilization, or partial remission, or even in a reduction of tumor mass <50% [15]. The investigators concluded that ^{90}Y-DOTATOC could be a powerful and promising new (adjuvant) therapeutic agent for anti-cancer treatment [15, 16]. However, data on use of ^{90}Y-DOTATOC in a neoadjuvant setting for treating hepatic metastases from NETs have not been reported to date. We therefore exploited the therapeutic potential of this novel therapy for down-sizing primarily non-resectable synchronous liver metastases in a patient with primary NET of the pancreatic tail.

The case

We report on a 49-year-old male patient (180 cm, 78 kg) who presented in our clinic with an advanced lesion of the pancreatic tail and concomitant multifocal hepatic lesions affecting both liver lobes. Uncharacteristic symptoms (i.e., nausea, abdominal pain) 2 months prior to admittance led to the initiation of diagnostic procedures by a gastroenterologist and included an esophagogastroscopy, abdominal magnetic resonance imaging (MRI), computed tomography (CT) and a SST-R scintigraphy. Results from imaging studies led to the diagnosis of a NET of the pancreatic tail (5×3 cm) with multiple (>6) synchronous bilobular liver metastases (<5 cm) and exhibiting a strong SST-R-positivity (Fig. 1). CT-guided needle biopsy of one of the hepatic lesions revealed a moderately (G2) differentiated NET with staining positivity for chromogranin A, neuron-specific enolase (NSE), and synaptophysin. Importantly, extra-abdominal lesions, suspicious for metastatic disease, were not detectable. In addition, the serum tumor marker NSE was elevated (32 ng/ml), whereas CEA, CA 19-9, β2-microglobulin, alpha fetoprotein and prostate-specific antigen were within physiologic ranges. Besides an erosive gastritis of the antrum and a mild gastroesophageal reflux disease, the patient was in a good health condition with no clinical symptoms of a hormonally active NET, gastrinoma, or MEN-I disease.

Therapy concept

Based on the SST-R positivity of this metastatic NET of the pancreatic tail, with strong tracer storage in the hepatic lesions (n>6), a therapeutic approach using ^{90}Y-DOTATOC was considered. ^{90}Y-DOTATOC therapy has recently proven promising efficacy for metastatic NET [13, 14]. However, due to the co-existing large tumor located in the pancreatic tail, we hypothesized that ^{90}Y-DOTATOC therapy may be more efficient, in terms of achieving a clinical response of hepatic metastases, when the primary

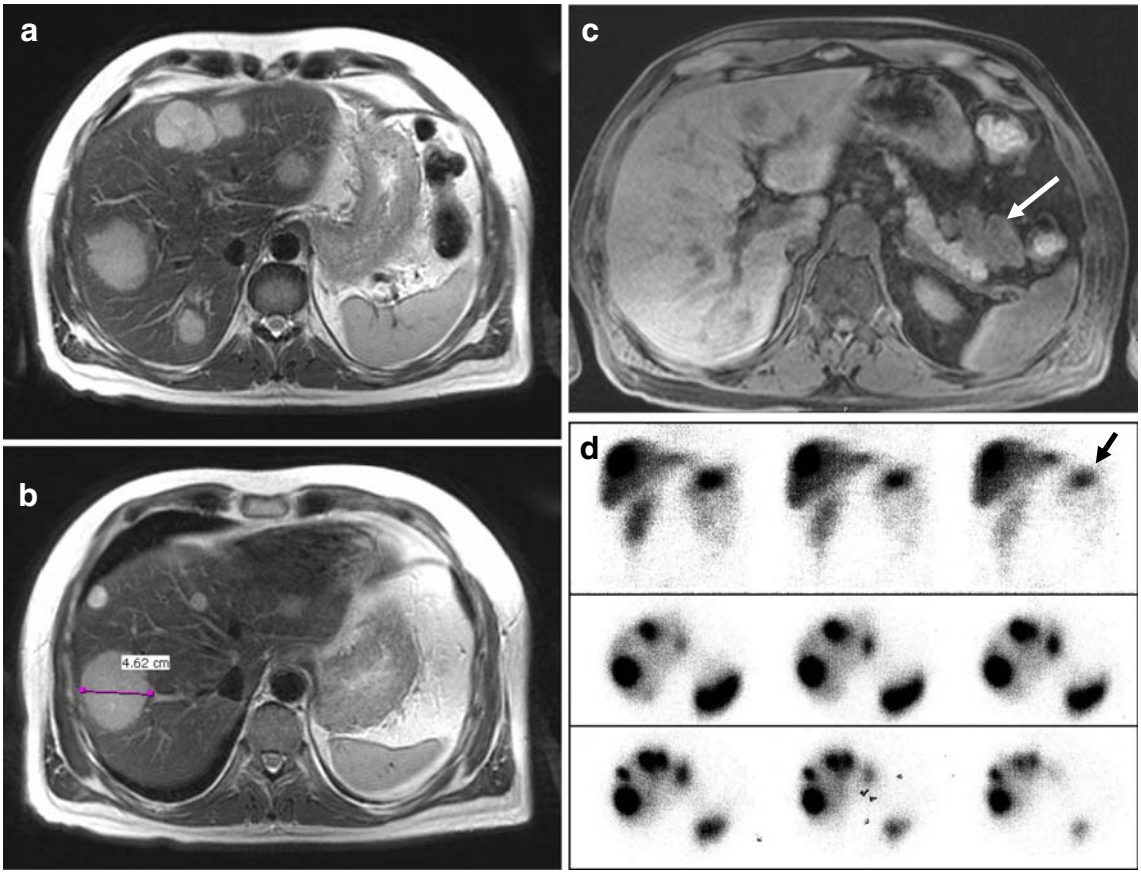

Fig. 1 Neuroendocrine tumor of the pancreatic tail with hepatic lesions. **a**–**c** Preoperative MRI imaging of hepatic lesions and the primary NET of the pancreatic tail (*arrow*). The largest hepatic lesion was fond in the right liver lobe (4.62 cm in diameter). **d** SMS scintigraphy showed multiple (>6) SST-R-positive hepatic lesions and one lesion in the perisplenic area (*arrow*) that corresponded to the primary tumor

tumor would first be resected prior to ^{90}Y-DOTATOC treatment. In addition, ^{90}Y-DOTATOC therapy was planned as a neoadjuvant concept for achieving potential resectability of liver metastases. The concepts of neoadjuvant therapy (i.e., conversion therapy) of primarily non- or marginally resectable liver metastases has proven efficacious in patients with colorectal hepatic metastases [17]. However, such neo-adjuvant approach has, to date, not been reported for a ^{90}Y-DOTATOC treatment of NETs. We therefore proposed a therapy concept using staged surgery with first resection of the primary tumor (pancreatic tail), followed by ^{90}Y-DOTATOC treatment of liver metastases and a second approach for potential surgical resection of remaining hepatic lesions (intended R0 resection).

Clinical course—pancreatic surgery

After routine preparation for abdominal surgery, we performed an explorative laparotomy using a transversal incision with extension into the epigastric midline to allow complete exposure of the upper GI tract, including the liver. However, the liver was only partially mobilized for performing an intraoperative ultrasound (IOUS) in order to avoid severe adhesion formation that could compromise the planned liver resection in the later clinical course. All hepatic lesions were documented by IOUS, and the clinical statement of "primarily non-resectable liver metastases" was confirmed. The pancreas was explored, and the primary NET of the pancreatic tail was resected by IOUS-guided en bloc left pancreatectomy with lymphadenectomy and splenectomy. The postoperative course of this patient was initially uneventful with no evidence of pancreatic fistula, and the patient was discharged on the postoperative day 8. However, a symptomatic fluid retention (fever, C-reactive protein increase) at the pancreatic resection line developed by day 15, which required CT-guided intervention for drainage placement and additional 5 days of hospital admission.

The final histopathological examination of the resected en bloc specimen revealed a 6.5×5.0×5.0 cm measuring tumor of the pancreas with encapsulated and nodular appearance. By microscopy, this solid tumor was defined as a malignant epithelial tumor of the endocrine pancreas with ten mitoses per 10 high power fields. In addition, a

vascular invasion was detected, and also the peri-pancreatic fatty tissue appeared to be infiltrated by this tumor. Overall, the tumor was classified as a well-differentiated NET of the pancreas.

Clinical course—neoadjuvant ^{90}Y-DOTATOC therapy

Eight weeks after pancreatic surgery, the patient received two single applications of ^{90}Y-DOTATOC therapy (195 mCi/m^2 per session; amino acid protection) in neoadjuvant intention, with an 8-week interruption of administrations [13, 16, 18]. After completion of ^{90}Y-DOTATOC treatment, the patient was enrolled in a tight follow-up program with repeated somatostatin (SMS) scintigraphy and MRI scans documenting good response. One year after the first treatment, no SST-R-positive metastases were detectable. Due to the lack of further remission of radiologically persistent liver lesions, a full re-staging was performed for evaluating resectability of these hepatic lesions. The MRI imaging documented a 50% regression of the largest tumor in the right liver lobe (Figs. 1a and 2a), and overall, an impressive remission of all hepatic lesions, as determined by (18)F-fluoro-deoxy-glucose (FDG) positron emission tomography (PET)-CT showing only one metabolically active tumor in the liver (Fig. 2b). In addition, one suspicious lesion was detected in the splenic fossa, suggesting local recurrence (Fig. 2c). Besides this particular (resectable) lesion, there was no evidence for additional extrahepatic tumor; hence, reviewing staging results conclusively led to the decision of liver resection (atypical/subsegmentectomy) with curative (R0 resection) intention.

Clinical course—hepatic surgery

After routine preparation for abdominal surgery, we performed an explorative laparotomy and fully mobilized the liver for facilitating IOUS in order to evaluate resectability of the hepatic lesions. In addition, the recurrent SST-R-positive tumor formation suspicious for residual disease in the splenic fossa/para-renal was completely resected (Fig. 2c). The hepatic lesions identified by IOUS

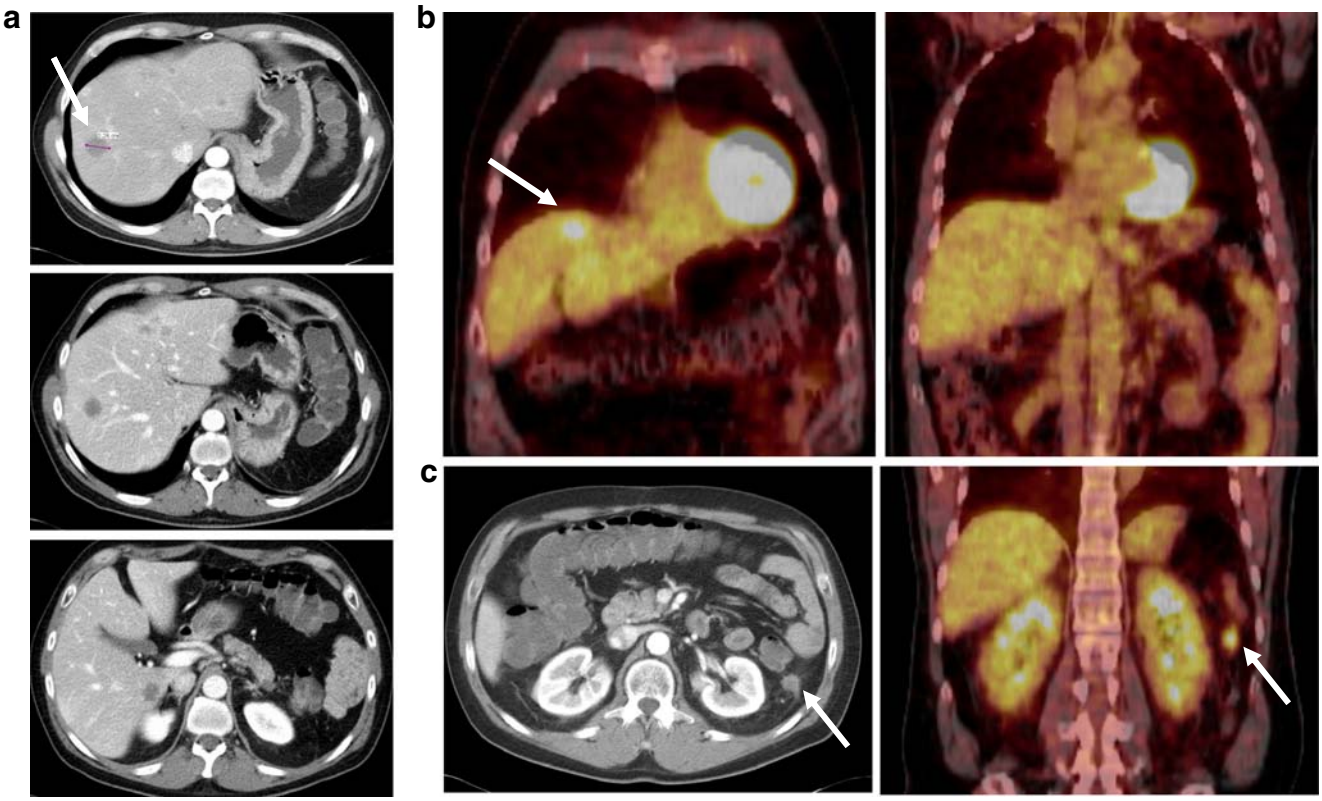

Fig. 2 Post-neoadjuvant ^{90}Y-DOTATOC therapy of liver metastases. **a** By computed tomography, hepatic NET lesions showed an impressive response to ^{90}Y-DOTATOC therapy after 1 year. The largest lesion in the right lobe was reduced to 2.3 cm in diameter (50% change). These hepatic lesions now appeared to be surgically resectable. **b** The PET-CT after ^{90}Y-DOTATOC treatment documented one metabolic active tumor in the liver (SVIII) (*arrow*) and no extrahepatic disease. **c** One additional lesion (recurrence) was detectable in the splenic fossa, which also was found to be PET positive (*arrow*). Similarly, this lesion was found to be surgically resectable

were resected in terms of multiple sub-segmental resections (n=8) in the regions SII/III/IVA/IVB/V/VII and SVII/VIII (Fig. 3a). One additional metastatic lesion in SV was ablated by intraoperative radiofrequency ablation (RFA) for technical reasons in order to avoid further loss of liver parenchyma (Fig. 3b). Moreover, this approach would allow repeated surgery on the right lobe in case of tumor recurrence in the future. A postoperative CT documented the resected areas without any remaining visible metastases (Fig. 3c). The postoperative course was uneventful, with no evidence of bile leakage, and the patient was discharged on the postoperative day 9.

The histopathological examinations of the resected liver specimens and of the splenic fossa tumor revealed metastases of a NET that, in general, corresponded to the resected primary lesion in the pancreatic tail. Both the primary tumor and the metastases showed typical neuroendocrine differentiation with solid cell sheets separated by broad fibrous bands and accompanied by numerous smalls sized vessels. They displayed slight nuclear atypia with coarse chromatin and only few mitoses (Fig. 4). Immunohistochemically, the lesions were positive for chromogranin A, but negative for glucagons, insulin, somatostatin, gastrin, and serotonin. There was a similar proliferation rate of ^{90}Y-DOTATOC-treated liver metastases and of the tumor arising in the splenic fossa, compared to the initial histology of the pancreatic tail NET (Fig. 4). However, these lesions elicited a slightly higher proliferating fraction (60%) than the ^{90}Y-DOTATOC-naive primary tumor in the pancreas (50%). At 1 year of follow-up, there was no evidence for tumor recurrence within the liver or pancreatic/splenic fossa by CT scan and SMS scintigraphy.

Discussion

In this report, we demonstrate the suitability of ^{90}Y-DOTATOC treatment in a neoadjuvant therapy concept for down-sizing hepatic metastases from a SST-R-positive NET of the pancreatic tail. An impressive partial response of this therapy regimen led to resectability of all hepatic lesions, including RFA ablation of one deep intraparenchymal located lesion. To our knowledge, this is the first report on the use of ^{90}Y-DOTATOC preoperatively, i.e., neo-

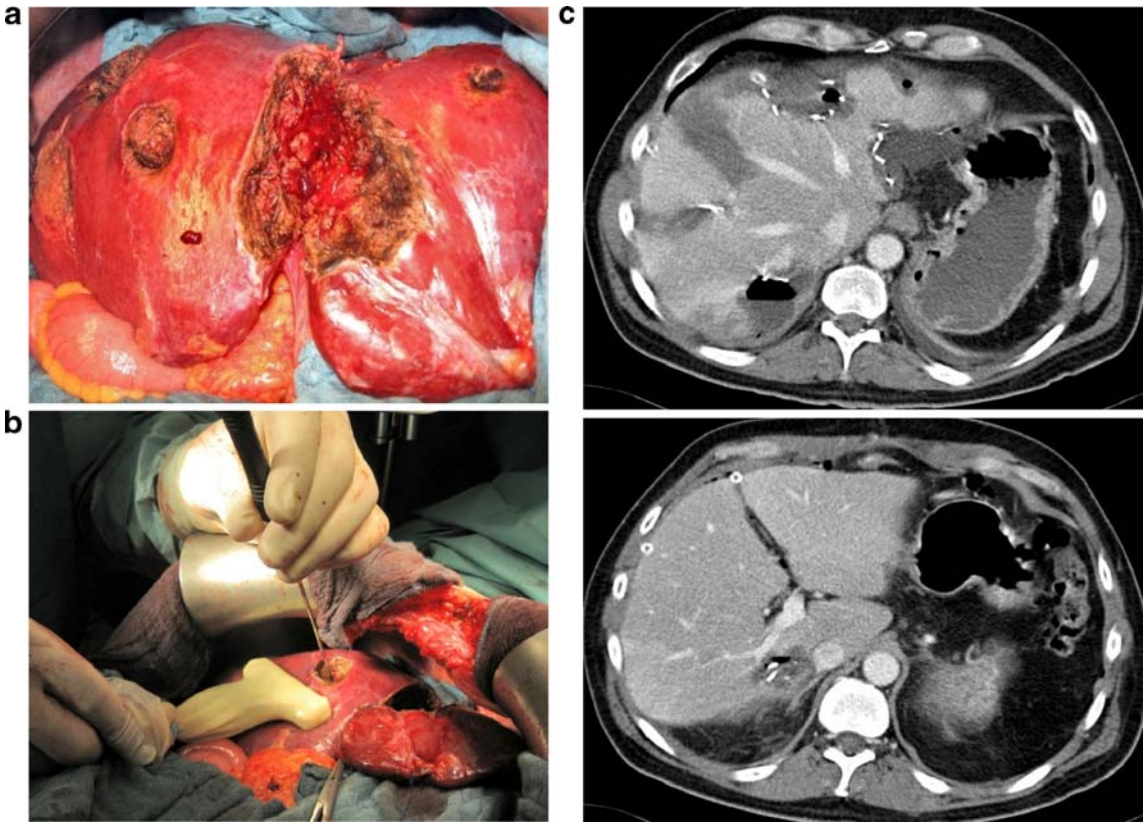

Fig. 3 Status post-liver resection and radiofrequency ablation. **a** Intraoperative image after multiple subsegmental ultrasound-guided liver resections. All lesions identified by ultrasound were resected. **b** One remaining central hepatic lesion was ablated using the radiofrequency probe (RFA/RITA) to reduce additional loss of parenchyma. **c** The postoperative CT scan did not detect any remaining tumor lesions and documented a regular post-surgical status

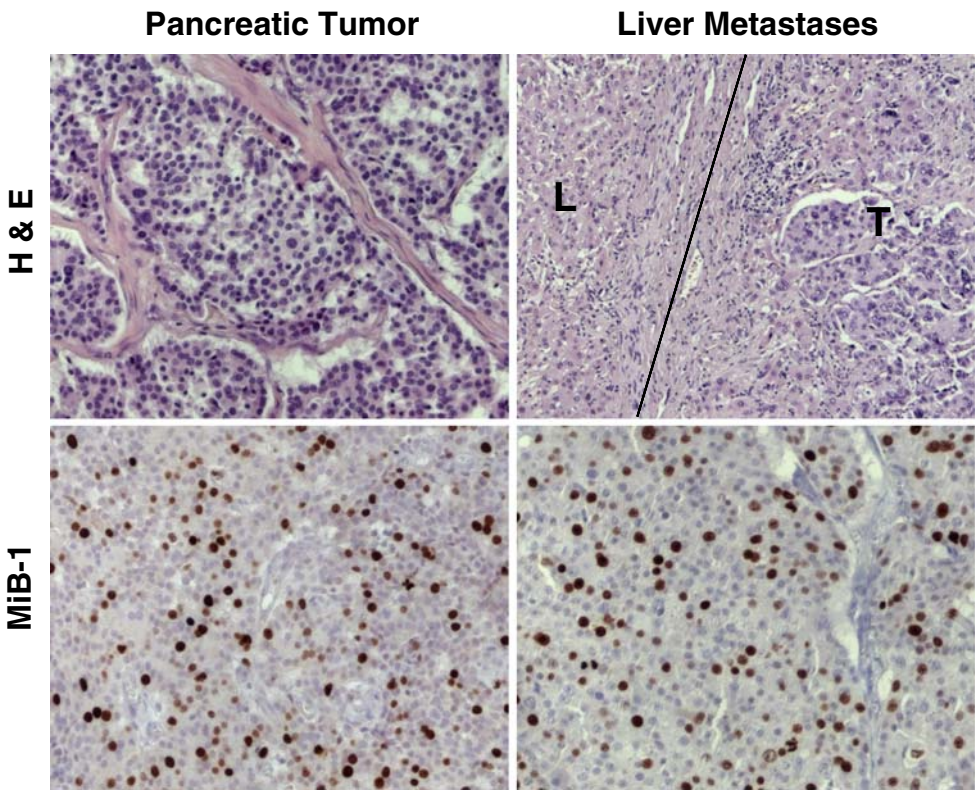

Fig. 4 Histology of liver metastases versus primary tumor in the pancreas. Histological analysis of the primary ^{90}Y-DOTATOC-naive pancreatic tumor (*left panel*) and ^{90}Y-DOTATOC-treated hepatic NET (*right panel*). H&E (*upper row*) and MiB-1 staining (proliferation) is demonstrated for the primary tumor and metastasis (×20) showing a comparably high proliferation rate in the primary tumor and the liver metastases

adjuvant intention, prior to liver resection, a novel concept that needs to be further validated in clinical studies.

With this staged and neoadjuvant therapy concept, we achieved radical resection of all hepatic NET lesions and simultaneously preserved a substantial amount of healthy liver parenchyma. In view of the fact that these NETs, in general, have a high probability of recurrence, we chose this particular parenchyma sparing approach for facilitating potential extended liver resections (i.e., hemi-hepatectomy) in the future clinical course of this patient. In addition, we speculate that recurrence rates of NETs after neoadjuvant ^{90}Y-DOTATOC treatment may be distinct to those not receiving this conversion therapy; however, this speculation needs to be proven in a future study with higher numbers of patients. In view of the low incidence of this malignancy, only a multi-center study will be able to answer these questions. Nevertheless, in our study, we observed an impressive response of hepatic NETs metastases to neoadjuvant ^{90}Y-DOTATOC treatment, thus leading to a reduction by 50% of the largest tumor in the right liver lobe. Such response rate has similarly been reported for other NETs [13–16, 18]. In a study on 20 patients with metastatic non-resectable NET (i.e., NET of pancreas, midgut, gastrinoma, paraganglioma, or NET of unknown primary origin), Frilling and colleagues [16] reported that ^{90}Y-DOTATOC therapy led to a partial remission in five patients and stabilized the disease in 11 patients, whereas tumor progression under this therapy occurred in four patients, suggesting that, in view of response rates, a second surgical intervention could be considered in selected cases. To date, treatment of patients with advanced and metastatic NETs is not well-defined or straightforward. A radical resection of pancreatic NETs has only been advocated for patients without evidence for metastasis. In contrast, other reports exist where using an individualized therapeutic approach in terms of radical resection of the primary tumor and subsequent liver transplantation have been performed for achieving an R0 situation in selected patients with NETs [4, 5, 11]. On the other hand, it has been recommended that patients with metastatic NETs receive palliative therapy or best supportive therapy. Hence, with the novel option of ^{90}Y-DOTATOC therapy for selected patients with SST-R-positive advanced NET, we suggest that patients receiving such therapy should be re-evaluated for surgical intervention, as radical resection remains the best curative option for these patients. With this report, we now provide some evidence that staged surgical concepts combined with neoadjuvant ^{90}Y-DOTATOC therapy could be valuable for such patients.

Importantly, as is evident in the MRI images of our patient, the resection line for R0 resection of the largest lesion also was changed by this therapy, hence facilitating an atypical/segmental resection. This finding is in concordance with observations in patients receiving neoadjuvant therapy of primarily non- or marginally resectable colorectal liver metastases, where the initially defined resection lines

had changed upon the course of down-sizing/neoadjuvant therapy. Hence, these neoadjuvant approaches could help save healthy liver parenchyma, which will be favorable for future liver resection in the case of tumor recurrence. Another important aspect of preoperative staging is the observation that, after neoadjuvant ^{90}Y-DOTATOC therapy, only one lesion was positive in FDG-PET-/SST-R scintigraphy, whereas the histological evaluation of resected liver metastases revealed vital tumor tissues in all resected specimens.

Nevertheless, this issue of vital tumor tissues raises the question of adequate staging and imaging of advanced NETs and certainly in the course of such neoadjuvant therapy [19, 20]. Sundin and colleagues [20] recently reported that 5-hydroxy-L-tryptophan (5-HTP) PET (C5-HTP-PET) proved better than CT and SST-R scintigraphy by visualizing additional small lesions, suggesting that this imaging is superior to FDG-PET, as only dedifferentiated NET will uptake FDG. Similarly, the use of (18)F-L-DOPA-PET has been advocated for staging of NET, as it performs better than SST-R scintigraphy in visualizing NETs [19]. Therefore, the definition of an optimal staging procedure for NET remains challenging and requires multi-disciplinary communication. Based on this literature, we would suggest the routine use of MRI and CT to define local surgical resectability and additional functional tests (i.e., C5-HTP-PET, SST-R scintigraphy, L-DOPA-PET, ^{90}Y-DOTATOC-PET) for detecting distant metastases and monitoring efficacy of neoadjuvant ^{90}Y-DOTATOC therapy. However, the value of these diagnostic approaches has also to be addressed in larger studies.

In conclusion, neoadjuvant ^{90}Y-DOTATOC therapy appears to be a valuable option for patients with SST-R-positive advanced pancreatic NETs metastatic to the liver, thus facilitating curative liver surgery. In our opinion, this concept warrants further investigation in clinical studies. Importantly, multi-disciplinary approaches in staging, diagnosis, and treatment are required for identifying suitable patients for this novel concept.

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