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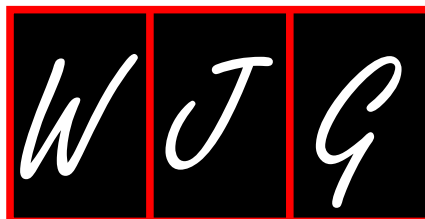
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Role of surgery in pancreatic cancer

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Abstract

Treatment of pancreatic cancer is multimodal and surgery is an essential part, mandatory for curative potential. Also chemotherapy is essential, and serious postoperative complications or rapid disease progression

may preclude completion of multimodal treatment. The sequence of treatment interventions has therefore become an important concern, and numerous ongoing randomized controlled trials compare clinical outcome after upfront surgery and neoadjuvant treatment with subsequent resection. In previous years, borderline resectable and locally advanced pancreatic cancer was most often considered unresectable. More effective chemotherapy together with the latest improvements in surgical expertise has resulted in extended operations, pushing the borders of resectability. Multivisceral resections with or without resection of major mesenteric vessels are now performed in numerous patients, resulting in better outcome, recorded as overall survival and/or patient reported outcome. But postoperative morbidity increases concurrently, and clinical benefit must be carefully evaluated against risk of potential harm, associated with new comprehensive multimodal treatment sequences. Even though cost/utility analyses are deficient, extended surgery has resulted in significantly longer and better life for many patients with no other treatment alternative. Improved selection of patients to surgery and/or chemotherapy will in the near future be possible, based on better tumor biology insight. Clinically available biomarkers enabling personalized treatment are forthcoming, but these options are still limited. The importance of surgical resection for each patient's prognosis is presently increasing, justifying sustained expansion of the surgical treatment modality.

Key words: Adjuvant chemotherapy; Neoadjuvant chemotherapy; Metastasis; Pancreatic cancer; Patient reported outcome; Survival

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Core tip: Both surgery and chemotherapy are mandatory in multimodal treatment of pancreatic cancer to obtain curative potential. The sequence of interventions is a core question: Upfront surgery or neoadjuvant chemotherapy with subsequent resection.

Also the role of extended operations incorporating reconstruction of major mesenteric vessels and multi-visceral resections is a matter of ongoing evaluation. The current direction of this development is increasing prognostic importance of surgical resection.

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INTRODUCTION

What should be the first treatment intervention in a patient with resectable pancreatic cancer (PC), surgery or chemotherapy? This is currently a core question for clinicians and patients, as standard of care is multimodal treatment, necessitating both^[1,2]. Increasing numbers of patients with borderline resectable or locally advanced tumors undergo resectional surgery, often after neoadjuvant chemotherapy^[3,4], but in metastatic disease palliative chemotherapy without resectional surgery is standard of care^[5]. Surgical expertise is rapidly improving due to technological development, reorganization of patient management and above all; better training of surgeons^[6,7], and the role of surgery in the multimodal treatment algorithm is revised continually^[8]. Available evidence and ongoing trials focusing the role of surgery, is summarized below, together with future topics of research and development.

CLARIFICATION OF CONCEPTS - SELECTION OF ENDPOINTS

Even though the purpose of resectional surgery is complete removal of the tumor (R0 resection), the distinction from R1 status (residual microscopic disease) is controversial. The first problem is two different R0 definitions, zero mm^[9] versus one mm^[10] tumor free margin. Second, divergence in pathology specimen examination is widespread even though a standardized protocol for examination of pancreaticoduodenectomy specimens was clearly described ten years ago^[10]. Also the dispersed tumor growth in PC^[11] and morphological heterogeneity in ductal adenocarcinoma of the pancreas^[12] contribute to incomparable data on R0 rates from different surgical centers. Rate of R0 resection is therefore an inappropriate endpoint in clinical studies, particularly after neoadjuvant chemotherapy. The tumor does not necessarily shrink from the periphery, but spot wise, and no clear definition of R0 status after neoadjuvant chemotherapy exists.

The rate of surgical resection after neoadjuvant treatment is another parameter, inappropriate as

endpoint in the evaluation of putative treatment benefit. In patients with a resectable tumor, the rate of resection decreases after neoadjuvant chemotherapy, as some patients become unresectable due to progressive disease. But in patients with borderline resectable or locally advanced tumors, resection rates are supposed to increase after neoadjuvant treatment, even though the resection rate does not yield core information on treatment significance.

The ultimate quality indicator of pancreatic surgery is clinical outcome in operated patients^[13], and only trials with overall survival (OS) and patient reported outcome (PRO)/quality of life (QoL) as endpoints can generate valid evidence, clarifying the role of surgery in the study population^[2,14].

PRIMARY RESECTABLE TUMORS

Neoadjuvant chemotherapy has been advocated in patients with resectable tumors to secure completion of systemic treatment^[15] which may be precluded by postoperative complications or early disease progression after upfront surgery^[16]. The net result of neoadjuvance is selection of patients with favorable tumor biology for subsequent resection. However, single center studies^[15,17] with median OS in the range 36-44.9 mo in this selected group, have left questions on the clinical consequences for the residual group mostly unanswered. Mokdad *et al*^[18] described median OS 26 mo in 2005 patients, operated after neoadjuvant chemotherapy compared to median 21 mo in 6015 patients after upfront surgery. However, this comprehensive report from the National Cancer Data Base for the years 2006-2012 is based on the same selection bias - still avoiding focus on outcome of conservative treatment. Metaanalysis, mainly based on retrospective studies, have not documented survival differences in patients operated upfront vs after neoadjuvant chemotherapy^[19], and randomized controlled trials (RCT) are mandatory. Currently accepted consensus is that patients with resectable tumors should undergo upfront surgery and subsequent adjuvant chemotherapy^[1]. However, numerous RCTs are running, one is the PEROPANC trial, opened April 2013 with endpoint OS^[20], and new evidence enabling improved clinical practice is foreseen within the near future.

At present, significant alterations of treatment sequences take place outside clinical trials. In the US, neoadjuvant chemotherapy is increasingly favored^[21], whereas the European preference tends to be upfront surgery^[22,23]. In line with the European strategy, different adjuvant regimens have been evaluated, and addition of Capecitabine to Gemcitabine was recently found to increase median survival to 27 mo in the ESPAC 4 trial^[24]. This is at present standard of care, but evaluation of even more effective antitumor regimens are under evaluation in ongoing trials, and

a scenario with second line treatment as an option in case of recurrent/progressive disease postoperatively seems to be in the pipeline. Adjuvant immunotherapy with RAS-peptides has been found to generate long term immunological memory, documented in a phase I/II study in 23 patients after resection of pancreatic ductal adenocarcinoma (PDAC)^[25] with no other adjuvant treatment. Five year survival was 22%, ten year 20%. In the ESPAC 1 study, including patients during approximately the same time interval, median survival without any adjuvant chemotherapy was median 8 mo, and adjuvant RAS vaccination seemingly increased survival. The clinical benefit of adjuvant immunotherapy it probably going to play an important role in the future^[26], even though it is not standard of care yet. But in this setting, removal of the primary tumor is crucial in order to avoid the effect of inhibitory regulatory T-cells^[27]. This perspective is favoring upfront surgery.

BORDERLINE RESECTABLE AND LOCALLY ADVANCED PANCRATIC CANCER

Borderline resectable tumors have been clearly defined radiologically^[28,29], and the possible benefit of neoadjuvant chemoradiation in this group was published by Katz *et al*^[30] 2008. Subsequently, the ability to stabilize metastatic PC has been demonstrated for FLFIRINOX in 2011^[31], then gemcitabine plus nab-paclitaxel in 2013^[32], both highly relevant regimens also for neoadjuvant evaluation. A meta-analysis including 13 studies on FOLFIRINOX-based neoadjuvant therapy in a total of 253 patients with borderline resectable (BRPC) or locally advanced pancreatic cancer (LAPC) tumors, described median survival in the range 13.7 to 24.2 mo^[3]. The Heidelberg group has recently published outcome in 575 LAPC patients all receiving neoadjuvant treatment and restaging between December 2001 and June 2015^[4]. In 125 patients, receiving neoadjuvant FOLFIRINOX, successful resection was possible in 76 (61%). Median OS in resected patients was 15.3 mo vs 8.5 mo after exploration alone. This information strongly support active multimodal treatment of BRPC and LAPC patients, as permanent cure seems achievable for some patients, also in these groups.

METASTATIC DISEASE

Metastatic PC (M1) is conceived a palliative condition in which surgical resection is contraindicated^[5,29]. Curative intent surgery (resection of primary tumor and metastases) has been evaluated in 29 M1 patients, published 2007. Median OS was 13.8 mo, one year survival 58.9%^[33], supporting the conservative guidelines. However, in a recent report 128 patients, undergoing resection of the primary

tumor and metastases, OS 12.3 mo and 10% five year survival was obtained^[34]. In another prospective study 11 patients obtained median OS 39 mo after resection of the pancreatic tumor and metastases^[35]. Recent evidence also suggest that patients with only pulmonary metastases is a subgroup with better prognosis^[36], and selected M1 patients seem to benefit from surgical resection.

When M1 disease can be stabilized with chemotherapy and local tumor growth does not preclude resection, reassessment of resectability should be offered, as shown from Heidelberg: In 575 LAPC patients, receiving neoadjuvant chemotherapy, M1 disease was the primary reason for unresectability in 135 patients (23.5%). Resectional surgery almost doubled OS in this cohort, compared with chemotherapy alone. A new window of opportunity seems to open for patients with metastatic PC, when stable disease can be achieved by neoadjuvant treatment.

SURGERY IN RECURRENT DISEASE

Also postoperative recurrence of PC has been conceived as a palliative condition with no indication for surgical intervention. New evidence suggests that a modification of current practice is required. In 57 patients with histologically proven local recurrence, surgical resection of the isolated local recurrence was possible in 41 (72%), resulting in median OS 16.4 mo, compared to median 9.4 mo in the 16 patients (28%) after exploration only^[37]. Increased survival after repeat pancreatectomy of local recurrence have also been reported from Japan^[38] and this procedure can be successfully performed laparoscopically^[39]. In pulmonary recurrence, long term survival after resection of metastases has recently been reported^[36]. New chemotherapeutic regimens with improved response rates^[31,32,40] seem to open new windows of opportunity for surgical interventions with curative intent, when recurrent disease can be stabilized.

SURGICAL DEVELOPMENT

After reorganization of care for PC patients into multidisciplinary centers with high patient volume for single surgeons and hospitals, postoperative morbidity and mortality has been significantly improved^[41-45]. But extended operations have concurrently been offered more patients, combining resection/reconstruction of major mesenteric vessels and multivisceral resections (MVR)^[46]. This development has increased postoperative morbidity but not mortality^[47]. Clinical benefit has been documented as a result of this expansion for the surgical part of PC treatment. Burdelski *et al*^[48] found median OS 16 mo after MVR in 55 patients vs 6 mo in 154 patients after palliative bypass ($P < 0.001$). Sahakyan *et al*^[49] reported median OS 20.3 mo and 3 year survival 26.3% after extended distal laparoscopic resection of advanced

PDAC. Selection of patients for these comprehensive procedures and prospective registration of survival and PRO is mandatory to guide future development.

CONCLUSION

The role of surgery is changing and altering resection rates result in better clinical outcome for some, worse for others. Improved patients selection is therefore essential. In this matter, the general scarcity of biomarkers enabling prediction of treatment outcome is a major problem. Prospective clinical trials, based on available diagnostic tools are running, and will in the near future enable evidence based update of treatment guidelines. The current direction of this development is increasing prognostic importance of surgical resection.

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