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Pancreatic cancer

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ABSTRACT

The need for a common education and training track in surgical oncology across Europe has been emphasized. ESSO provides several hands-on courses for skills training and face-to-face discussions. The core curriculum provides a framework for the overall theoretical requirements in surgical oncology. The UEMS/EBSQ fellowship exam is designed to test core competencies in the candidate's core knowledge in their prespecified area of expertise. A core set of points for each cancer type is lacking. Hence, a condensed outline of themed expected to be covered in the curriculum and relevant to an optimal practice in surgical oncology is provided. This article outlines pancreatic cancer.

1. Introduction

There is a need to unify knowledge and skills in surgical oncology across Europe. To this end, a core curriculum in surgical oncology has been updated [1], providing a dense, point-by-point outline of central aspects of cancer care that the cancer surgeon should have expressed knowledge about. Notably, this dense lexicon may serve as a broad guide for studies in cancer surgery. However, there is a need to have further vetted input about the specific cancers, such as 'pancreatic cancer'. In this article, referral to a 'student' is regarding both trainees and specialist surgeons, as the training background varies considerably and the curriculum is hence directed towards both junior trainees and specialist surgeons who pursue a career in cancer surgery. All surgeons are life-long students - in theory and in practice.

The education and training in pancreatic surgery is not uniform across Europe nor the World [2]. The diagnosis and management of any specific cancer type is known to experience trends in knowledge, emerging challenges, ongoing debates and, a change in the knowledgebase from which both decisions and discussions are generated. Some of these are expressed in the form of consensus documents [3], other topics or debates may seem more nebulous as themes emerge in meetings or conferences. For the junior student, it may be a difficult task to grasp the overview of core themes in any given cancer subdiscipline.

Hence, based on the European fellowship exam candidates request, we have prepared an essential set of themes to present a set of core knowledge needed for a specific disease beyond the core curriculum in surgical oncology. This will not be a textbook, nor a comprehensive review. Rather, it should provide an overview of themes and associated references for further study, but with more detail than the core curriculum overview [1]. Here, we present the knowledge and emerging evidence in the field of pancreatic cancer.

2. Epidemiology, risk factors and early diagnosis

Pancreatic cancer is increasing in most parts of the Western world. In general, pancreatic cancer is less common than many other large cancer groups, but due to an increasing incidence in an aging population, and the high lethality rate, it is rapidly becoming one of the most frequent causes of cancer deaths [4,5].

Known risk factors are related to lifestyle characteristics such as smoking, alcohol consumption and overweight [5]. The overall strongest risk factor is increasing age. Chronic and hereditary pancreatitis are known risk factors to pancreatic cancer. Hereditary pancreatitis is related to genetic risk, and both familial pancreatic

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cancer and genetic syndromes are associated with a higher incidence of pancreatic cancer [4,6–8]. New-onset diabetes is increasingly appreciated as an early warning sign [9], although screening recommendations are not yet clear. Cystic lesions are a risk factor for pancreatic cancer [10], and largely refers to mucinous cysts (mucinous cystic neoplasia (MCN) or intraductal papillary mucinous neoplasia (IPMN).

Identification of families of genetic risk are increasingly important from a screening and early detection perspective [11–13] and, also, as targeted drugs may be directed to those with a BRCA1/2 mutational profile. Pancreatic cancer developed on a background of hereditary non-polyposis colon cancer (HNPCC/Lynch syndrome) may be important as cancers with microsatellite instability may be rare responders to immunotherapy. Olaparib is currently approved in the metastatic setting for BRCA1/2 mutants, and ongoing trials are underway on use of this in the adjuvant setting. The treatment landscape for pancreatic cancer is evolving with new treatment approaches [14]. Guidelines [15,16] should be consulted in addition to updates from trials.

3. Precursor lesions and premalignant cysts

Precursors to pancreatic cancer occur, in practical terms, in the form of pancreatic cysts [17]. Cysts have become an increasing workload for surgeons involved in pancreatic diseases. A refined approach in choice of diagnostics and choice of surveillance over surgery is important [10], with changing perceptions with emerging data, and new knowledge accumulating in new guidelines. Specific guidelines have been proposed, yet varies considerably in recommendations [18]. The fellowship exam candidate should be able to know and discuss the core principles of cyst detection, management, surveillance and indications for surgery [10].

The candidate should also be aware of the role of Pancreatic Intraepithelial Neoplasia (PanINs) as the morphological component in the progression model of pancreatic cancer [4]. The distinction of PanIN to cystic precursor lesions, such as IPMN, should be clear.

4. Understanding the pathobiology of pancreatic cancer

Both the adjustable and genetic risk factors insufficiently explain the aetiology of pancreatic cancer [4]. However, increased risk ratios have been reported in patients with germ line mutations and hereditary disorders with exposure to environmental carcinogens. Therefore, a better understanding of the pathobiology is essential for its prevention and choice of treatment. Basic knowledge of pancreatic carcinogenesis includes the important RAS-pathway, including mutations in KRAS (found in >95% of all pancreatic cancers), CDKN2A, TP53, and SMAD4 [4,5]. The carcinogenesis evolves morphologically in the pancreatic duct through the pancreatic intraepithelial neoplasia (PanIN) precursors and subsequent malignancy with tumor spread into the local and distant microenvironment. Knowledge on the unique features of stromal proliferation and metabolic adaptation to obtain nutrients in a hypoxic environment and inherent chemoresistance is important in this regard [4,19]. Moreover, these driving mutations play an increasing role in diagnosis with the use of high-throughput DNA analyses.

5. Staging and the evolution of borderline and locally advanced disease

Appropriate staging is an important part of classifying disease and choosing appropriate treatment. Staging as based on clinical, radiological, laboratory/biomarker and pathological examinations should be incorporated into a comprehensive understanding of strengths and pitfalls [20]. Borderline resectable and locally advanced pancreatic cancer is defined by several different systems [21–23], while the NCCN definition is the most frequently used [16]. Definition used for borderline resectable and locally advanced cancers is important for operation planning and for reconstruction alternatives [24] of vessels (Fig. 1) when needed [22,25]. The definitions used is also important for comparison of trials results [26], as slight deviation in inclusion and exclusion criteria hampers the head-to-head comparison between studies.

In pancreatic cancer, the technical definition of resectability staging prevails over the formal TNM classification in clinical practice [23,27]. Together with imaging features, tumour biomarkers and clinical fitness, the decision to pursue systemic therapy first, upfront surgery or simple palliative care is made. Decisions should be made in a multidisciplinary team setting [28].

6. Neoadjuvant and adjuvant treatment and trials

Optimal survival in pancreatic cancer is achieved through multimodal therapy (Fig. 2) for both resectable, borderline and locally advanced pancreatic cancer [29]. The treatment sequencing and best multimodal combination remains uncertain, as several trials are ongoing and robust data still awaited [30]. While neoadjuvant treatment is becoming the standard in the treatment algorithm of borderline and locally advanced pancreatic cancer [21], the role in primary or 'upfront' resectable pancreatic cancer is still debated [31–35]. Ongoing trials are exploring the option of so-called total neoadjuvant treatment (TNT) whereby the full length of treatment is given prior to surgery [36–38], rather than split into pre- and post-surgical treatment courses. Resection of 'oligometastatic disease' (e.g. a single liver metastasis) in pancreatic cancer (Fig. 2) is controversial [39]. In a few, select patients with good and durable response from pre-operative (induction or conversion) therapy, resection can be offered with reasonable outcomes [40].

Basic knowledge about chemotherapy should include arguments in favour of neoadjuvant chemotherapy and upfront surgery, respectively, taking into account local staging by imaging, biological status (i.e. high CA19-9), need for biliary stenting, and patient performance status (Fig. 2). For preoperative chemotherapy, a tissue-diagnosis is required and hence either ERCP or EUS (or both) are required for tissue samples and for placing a stent to relieve of jaundice prior to oncological treatment [41]. Procedure related complications may occur (e.g. ERCP-induced acute pancreatitis) and should be acknowledged in the risk/benefit consideration. Preoperative stenting of the jaundiced patient should not be done as a routine in otherwise resectable tumours [42], unless infectious complications occur or neoadjuvant chemotherapy is planned. All pre-operative imaging should be done before any stenting of the biliary tract, if possible, to obtain high-quality staging.

The literature on the effect of adjuvant chemotherapy is well-documented, among others through the ESPAC1-4 and PRODIGE trials [43–46], that supports the routine use of adjuvant chemotherapy after surgery, with the most recent trial on modified FOLFIRINOX (fluorouracil, irinotecan, leucovorin, oxaliplatin) compared to Gemcitabine monotherapy presenting a median overall survival of almost 55 months for mFOLFIRINOX (compared to 36 months for Gemcitabine-based treatment) [45].

Intraoperative radiotherapy is controversial and only used at few centres in the setting of potentially curable or operable pancreatic cancer [47,48]. Trials on targeted therapy are ongoing and there is some evidence that certain pancreatic cancer subtypes may respond better to such treatment [30,49].

The majority of patients starting on 'induction or conversion' chemotherapy for locally advanced (or, oligometastatic) pancreatic

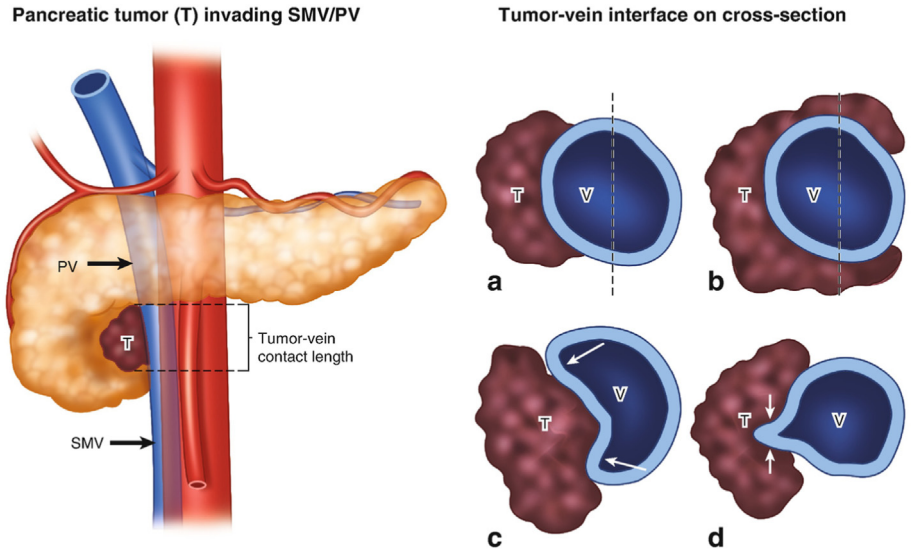

Fig. 1. Borderline resectability as defined by venous tumor contact
Legend: Venous tumor contact in pancreatic cancer invasion of SMV/PV. (**a**) Less than or equal to 180° tumor contact without deformity. (**b**) More than 180° tumor contact without deformity.
(**c**) Less than or equal to 180° tumor contact with deformity (arrows). (**d**) Tear drop deformity (arrows). *SMV* superiomesenteric vein, *PV* portal vein, *T* tumor, *V* vein. *Dashed line* 180° of lumen circumference. Reproduced with permission from Kleive et al. [25], ©Springer.

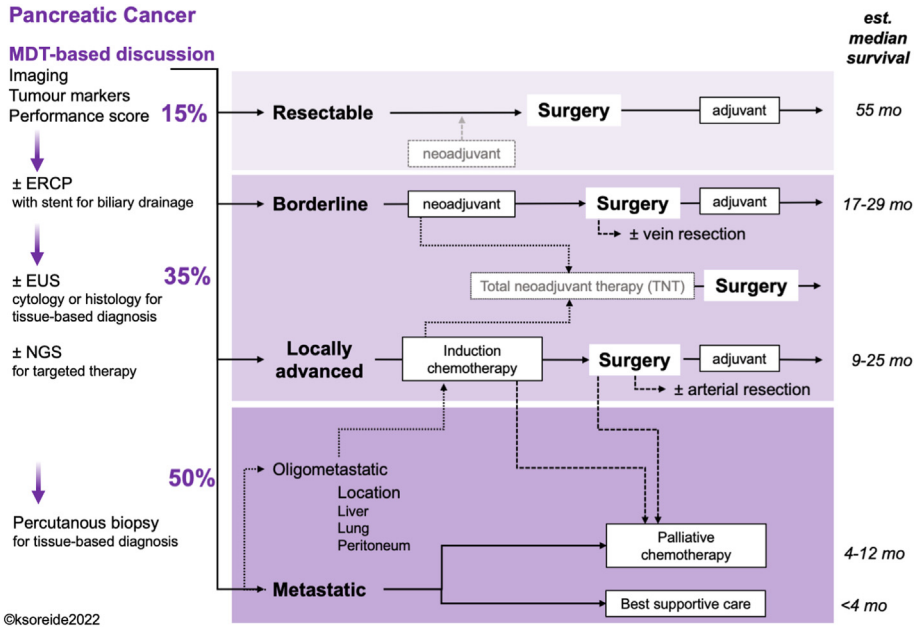

Fig. 2. Overview of contemporary concepts of multimodal therapy in pancreatic cancer
Legend: Different settings for resectable, borderline, locally advanced and metastatic pancreatic cancer. Adjuvant therapy after surgery is the standard in upfront resectable disease, but trials are exploring the role of 'neoadjuvant' therapy. Total neoadjuvant therapy (TNT) is an emerging concept, used for all categories. A subgroup of borderline and locally advanced proceed to surgery. Estimated survival time (far right) are accumulated outcomes, but large variation and heterogeneity across studies exist.

cancer will progress and hence go on to palliative chemotherapy. However, a select number of patients have stable disease or response and can be surgically explored for potential resection.

7. Enhanced recovery and perioperative care

Knowledge on perioperative care is essential as these may impact the outcome of pancreatic surgery. Enhanced recovery after surgery (ERAS) principles should be known and guided towards those intended for pancreatic surgery [50,51].

Prehabilitation for high-risk patients before surgery has experienced an increased interest [52,53], particularly as more elderly, frail and comorbid patients present with technically resectable pancreatic cancer but borderline clinical reserves. Assessment of nutritial needs [54], including exocrine supplement, is important for optimal outcomes [55]. Home-based exercise programs and frailty assessment is clinically relevant for patients with pancreatic cancer [56–58].

8. Surgery and related complications

Pancreatic surgery is complex and knowledge about the various indications, the variation in techniques and the relevant associated complications is essential. Pancreatoduodenectomy [59], open and laparoscopic distal pancreatectomy [60,61] and total pancreatectomy [62] each have their own specific indications, contraindications, and short-term and long-term considerations to be aware of. The evolution of surgery for pancreatic cancer including some of the newer concepts of vessel resections and radical surgery is required knowledge [22,25,63,64], even if some of these procedures are only performed in select patients at very high-volume centres.

An overview of the indications, contraindications, potential benefits and limitations to minimal-invasive surgery is required [61,65–67]. Appreciation of the benefits and risks of enucleation procedures should be required. The variants of pancreatic head resection and the outcomes of trials exploring extended lymphadenectomy, pylorus-resecting or -sparing and advanced vascular techniques, including vein resection and the rare indications for arterial resection and reconstruction. As most centres will not perform such advanced procedures, there is still a need to have an overview of which patient may be eligible for such approaches.

Several modes of resection and repair exist [68–70], and knowledge including a broad overview of the most common techniques is expected [68,70,71]. The candidate should have sound knowledge on possible prevention, early recognition, and treatment of complications after pancreatic surgery, for both surgical and non-surgical issues [72]. Knowledge of the most recent consensus definitions exist for typical complications related to pancreatic surgery, including post-operative pancreatic fistula [73], post-pancreatectomy haemorrhage [74], delayed gastric emptying [75] chyle leak [76] and, more recently, post-pancreatectomy acute pancreatitis [77].

9. Long-term outcomes

Furthermore, diagnosis and treatment of long-term consequences of pancreatic surgery is necessary to enhance quality of life and decrease morbidity. There are a wide range of instruments available to measure quality of life (QoL) outcomes in pancreatic cancer surgical patients, although only few are disease-specific [78,79]. Most of the included studies reported no significant changes in QoL outcomes at short- or long-term follow-up [78,79]. Dietary or nutritional issues, diabetes or other complications may occur in long-term survivors.

10. Experimental or adjunct treatments

Some techniques are being explored for added value in treatment of pancreatic cancer, with lack of robust data to firmly guide clinical decisions. Ablation techniques including irreversible electroporation (IRE) [80,81] remains experimental but may have an interest in combination with immune therapy in future trials [82].

11. Key sources for further studies

It is imperative to seek new and updated knowledge as well as establish a study base of existing data for in-depth studies. The continued consensus work of the International Study Group of Pancreatic Surgery (ISGPS) should be recognized [24,54,69,70,73–76,83]. Available guidelines and consensus reports should be consulted [3,16,18,50,55,84,85]. There are several sources of updated information on pancreatic cancer, such as the “Map of Pancreatic Surgery” (freely accessible via www.evidencemap.surgery) [83]. For pancreatic cancer, an ESSO-endorsed “Textbook of Pancreatic Cancer” in 2 vol is available from Springer, some of which are cited here [2,25,28,86]. Continuous updates will also be possible through ESSO pre-conference HPB courses and HPB masterclass courses (www.essoweb.org). Similarly, courses may be offered through the European-African Hepatobiliary-Pancreatic Association (E-AHPBA).

Declaration of competing interest

None reported.

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