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Review

3rd St. Gallen EORTC Gastrointestinal Cancer Conference: Consensus recommendations on controversial issues in the primary treatment of pancreatic cancer

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Abstract The primary treatment of pancreatic cancer was the topic of the 3rd St. Gallen Conference 2016. A multidisciplinary panel reviewed the current evidence and discussed controversial issues in a moderated consensus session. Here we report on the key expert recommendations.

It was generally accepted that radical surgical resection followed by adjuvant chemotherapy offers the only evidence-based treatment with a chance for cure. Initial staging should classify localised tumours as resectable or unresectable (i.e. locally advanced pancreatic cancer) although there remains a large grey-zone of potentially resectable disease between these two categories which has recently been named as borderline resectable, a concept which was generally accepted by the panel members. However, the definition of these borderline-resectable (BR) tumours varies between classifications due to their focus on either (i) technical hurdles (e.g. the feasibility of vascular resection) or (ii) oncological outcome (e.g. predicting the risk of a R1 resection and/or occult metastases).

The resulting expert discussion focussed on imaging standards as well as the value of pretherapeutic laparoscopy. Indications for biliary drainage were seen especially before neoadjuvant therapy. Following standard resection, the panel unanimously voted for the use of adjuvant chemotherapy after R0 resection and considered it as a reasonable standard of care after R1 resection, even though the optimal pathologic evaluation and the definition of R0/R1 was the issue of an ongoing debate.

The general concept of BR tumours was considered as a good basis to select patients for preoperative therapy, albeit its current impact on the therapeutic strategy was far less clear. Main focus of the conference was to discuss the limits of surgical resection and to identify ways to standardise procedures and to improve curative outcome, including adjuvant and perioperative treatment.
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1. Introduction

The main topic of the 3rd St. Gallen European Organisation for Research and Treatment of Cancer Gastrointestinal Cancer Conference 2016 was the primary treatment of pancreatic cancer. Ductal adenocarcinoma of the pancreas is one of the most common causes of cancer-related death worldwide. Predictions for 2025 rank pancreatic cancer as the third-leading cause of cancer-related death in the European Union [1] and by 2030 as the second-leading cause of cancer-related death in both genders in the United States of America [2]. Prognosis is dismal with a life expectancy below 5% after 5 years [3]. The only proven chance for increased long-term survival or even cure consists in radical surgical resection followed by adjuvant chemotherapy [4,5]. However, less than 20% of the patients present with a localised tumour that is clearly resectable at the outset. Initial staging is used to classify localised pancreatic cancer as resectable or unresectable (locally advanced pancreatic cancer [LAPC]) with a large grey-zone of potentially resectable tumours between these two categories, which has led to the identification of a third category, the so-called borderline-resectable (BR) tumours. However, definition varies between different classification systems due to their focus on either technical hurdles (e.g. vascular resection) or oncological outcomes (e.g. predicted R1 resection) [6–10]. Therefore, the main focus of this conference was to discuss the limits of surgical resection and to identify ways to improve outcome—including optimised planning of the therapeutic strategy, more advanced surgical techniques as well as adjuvant or perioperative treatments.

A representative faculty of expert surgeons, medical and radiation oncologists, pathologists and gastroenterologists reviewed the current treatment recommendations in a panel session based on a moderated consensus process. The main interests were controversial issues that could not be easily resolved through the study of published evidence and guidelines. As in the St. Gallen Breast Cancer Conferences, the panel was asked to assess the available evidence and vote on recommendations using a pre-circulated set of questions. Here, we summarise the key discussion points of the panel members.

2. Methods

In preparation for the panel session, which was held on 12th March 2016 and involved 18 experts, existing guidelines [7,8,11,12] were used to identify areas of uncertainty in order to define the topics for debate. Over 100 questions were circulated between panel members, of which 68 were retained for the panel discussion. During the session, which was moderated by JZ and ML the panel members were asked to assess and comment on optimal care based on the existing data and to recommend treatment strategies as expert opinion. Panel members were given the opportunity to comment on the issues raised by the questions before and after an electronic vote. Here, we summarise the extent of agreement or disagreement of the panel members on specific topics.

Even though care was taken to invite a representative spectrum of panellists from relevant disciplines, the general applicability of their conclusions may be limited by an unequal distribution of disciplines and/or underrepresentation of some regions of the world (all panelists are co-authors). The ensuing statements are generally meant for reasonably fit patients without severe comorbidities. In clinical practice, some patients will not match the model and treatment decisions need to be adapted.

3. Staging

Accurate pretherapeutic imaging of the primary tumour is the key component of any treatment decision [13], in addition to the full assessment of the patient's clinical status, comorbidities as well as screening for distant metastases. Resectability and the surgical approach depend on tumour size and location, and—most importantly—is limited by involvement of regional blood vessels. Arterial abutment or venous occlusion not only have a technical impact on the surgical approach and the complication rate, but also affect prognosis [10].

For primary visualisation of the tumour, a dedicated pancreatic protocol computed tomography (CT) scan with submillimetre sections was chosen as the preferred method by most panel members (92%), with only 8% opting for mandatory magnetic resonance imaging (MRI) and/or endoscopic ultrasonography (EUS).

To evaluate the potential for resection, a dedicated multiphase pancreatic CT scan was unanimously voted as the preferred diagnostic method (100%), with no need for a second imaging modality if the tumour and the surrounding vessels were visualised appropriately (92%). If needed, MRI was preferred over EUS (75% versus 25%) as the additional imaging method. Image acquisition has to be performed carefully within a defined multiphase protocol with high resolution. The imaging report should follow the recently published consensus recommendations [13] (Table 1).

Routine laparoscopic staging in resectable cancer was not considered necessary by all but one of the panel members. However, laparoscopy would be performed by 38% of the panelists in patients with BR tumours, by 1/3 of the panel in patients with risk factors (e.g. pain or grossly elevated CA 19-9 levels potentially indicating subradiographic systemic disease [14–16]) and by 14% in all patients with left-sided tumours in the pancreatic tail or body because of the increased risk of peritoneal seeding in this population [17]. Thirty-eight percent would also perform laparoscopy before any neoadjuvant treatment, again with the aim to exclude peritoneal disease before starting multimodal therapy. Peritoneal lavage was deemed of no use by almost all panellists (94%), mainly because most (77%) would not change their surgical approach based on positive cytology alone.

Complete staging includes the search for distant metastases in liver and lung. Staging for lung metastases is preferably performed by CT scan (90%) and not by chest X-ray (0%). Imaging of the liver is usually included in the staging CT of the primary tumour with no need for an additional MRI (only 18% were in favour of an additional scan) and no role for ultrasonography (voted as 'not sufficient' by 62% with 38% abstentions). There was also no role for positron-emission tomography–CT (82%). If CT demonstrates 'small pulmonary nodules', virtually all panel members would neglect them if they are smaller than 5 mm (93%). Fifty seven percent would even neglect those that are smaller than 10 mm, a view supported by two retrospective series from the US using preoperative chest CT scans and clinical follow up of 374 and 329 patients, respectively. Indeterminate pulmonary nodules (IPN) [18] or subcentimeter pulmonary nodules (SCPN) [19] were detected in 49% and 18% of the scans with no statistically relevant difference in median overall survival (15.6 months with IPN versus 18.0 months without IPN and 16.1 months with SCPM versus 19.1 months without SCPN). IPN also had no significant impact on the rate of subsequent development of lung metastases (16% versus 13%). In fact, only

Table 1
Technical requirements, interpretation and reporting of pretherapeutic dedicated multidetector CT in pancreatic cancer.

Technical parameters (dedicated dual-phase pancreatic protocol with angiography)	
Scan type	Helical (preferably at least 16-detector rows)
Section thickness	Preferably submillimeter (0.5–1 mm)
Interval	Same as section thickness
Oral contrast agent	Neutral or low-Hounsfield units oral agent
Intravenous contrast agent	Preferably high iodine concentration, injection rate of 3–5 ml/s
Scan acquisition	- Pancreatic parenchymal phase at 40–50 s (shortly after arterial phase) - Portal venous phase at 65–70 s
Image reconstruction	- Axial 2–5 mm thickness - Multiplanar reformats in the coronal plane at 2–3 mm thickness (per institutional preference additional sagittal plane) - Maximum intensity projections or 3D volumetric thick sections for vascular evaluation
Morphologic evaluation	
Appearance	- Hypoattenuating, isoattenuating or hyperattenuating (in the pancreatic parenchymal phase) - Size - Location (head/uncinated or body/tail)
Pancreatic duct	Narrowing/abrupt cut-off with or without dilatation
Biliary tree	Abrupt cut-off with or without upstream dilatation
Arterial evaluation	
Superior mesenteric artery (SMA)	Present or absent - Degree of solid soft-tissue contact ($\leq$180° or >180°) - Degree of increased hazy attenuation/stranding contact ($\leq$180° or >180°) - Focal vessel narrowing or contour irregularity (extension to first SMA branch?)
Celiac axis	Present or absent - Degree of solid soft-tissue contact ($\leq$180° or >180°) - Degree of increased hazy attenuation/stranding contact ($\leq$180° or >180°) - Focal vessel narrowing or contour irregularity (present?)
Common hepatic artery (CHA)	Present or absent - Degree of solid soft-tissue contact ($\leq$180° or >180°) - Degree of increased hazy attenuation/stranding contact ($\leq$180° or >180°) - Focal vessel narrowing or contour irregularity (present?) (Extension to celiac axis or bifurcation of right/left hepatic artery?)
Arterial variant	Present or absent - Variant anatomy (accessory right hepatic artery, replaced right hepatic artery, replaced CHA, origin of replaced or accessory artery, others) - Degree of solid soft-tissue contact ($\leq$180° or >180°) - Degree of increased hazy attenuation/stranding contact ($\leq$180° or >180°) - Focal vessel narrowing or contour irregularity (present?)
Venous evaluation	
Portal vein (MPV)	Present, absent or complete occlusion - Degree of solid soft-tissue contact ($\leq$180° or >180°) - Degree of increased hazy attenuation/stranding contact ($\leq$180° or >180°) - Focal vessel narrowing or contour irregularity (tethering or tear-drop?)
Superior mesenteric vein (SMV)	Present, absent or complete occlusion - Degree of solid soft-tissue contact ($\leq$180° or >180°) - Degree of increased hazy attenuation/stranding contact ($\leq$180° or >180°) - Focal vessel narrowing or contour irregularity (tethering or tear-drop?)
Thrombus within vein	Present or absent (MPV, SMV or splenic vein)
Venous collaterals	Present or absent (location: around pancreatic head, porta hepatis, root of the mesentery or left upper quadrant)

Adapted from the Consensus Statement of the Society of Abdominal Radiology and the American Pancreatic Association (Radiology 270; 1:248–260, 2014)

increasing age was associated with SCPN and no single individual radiographic criterion of SCPN including number, size, calcification or contour had an impact on overall survival [19].

Of note, the discussion did not cover the imaging strategy within surveillance programmes for early detection of pancreatic cancer in individuals at increased risk which has been the topic of several recent publications [20–22].

4. Pretherapeutic bile-duct drainage

In patients with bile duct obstruction, placement of a biliary stent via endoscopy may be used to relieve

jaundice, albeit with some risk of procedural complications and a significantly increased risk of bacterial cholangitis [23] that might have a negative impact on the success of surgery [24].

Therefore, the majority of the panel (54%) felt that biliary drainage before primary surgery should generally be avoided and restricted to patients with signs of cholangitis or even to patients with cholangitis and grossly elevated bilirubin levels only. Most panel members (81%) would even avoid a stent altogether if tumour resection was possible within one week.

Prior to preoperative multimodal therapy stent placement was deemed useful in cholangitis, but not necessarily in patients with simple cholestasis and no signs of infection (64% pro drainage in all patients). Some additional 18% of the panellists would be more restrictive and place stents only if bilirubin levels were grossly elevated (10 × upper limit of normal (ULN)). In any case, bilirubin levels should be lowered to 1.5 × ULN if preoperative FOLFIRINOX is to be given.

The preferred type of stent is a short metal stent (54% versus 46% for a plastic stent) which is more expensive but has the potential for longer patency, a lower risk of cholangitis interfering with neoadjuvant treatment and—if short enough—can easily be removed during resection [25,26].

5. Adjuvant treatment

Removal of the primary tumour without any additional treatment results in 5 year survival rates of 8–12% [4,27,28]. Several randomised phase III trials [27–29] have shown that additional postoperative chemotherapy (CTx) after macroscopically complete resection (i.e. R0 and R1) with either gemcitabine or 5-FU consistently increases 5-year survival by at least 11% (up to 24.4% in one trial). In contrast, results with postoperative radiochemotherapy (RCTx) vary between trials, with some reports even suggesting a deleterious effect [30,31].

Final results of the multicentre randomised phase III ESPAC-4 trial were published by Neoptolemos *et al.* [32] shortly after the St. Gallen conference, demonstrating a further increase in median overall survival from 25.5 months in the gemcitabine arm to 28 months with a combination regimen of gemcitabine and the oral fluoropyrimidine capecitabine (hazard ratio (HR) 0.82, 95% confidence interval (CI) 0.68–0.98, p = 0.032). The 5-year survival estimates increased from 16.3% (95% CI 10.2–23.7) for patients randomised to gemcitabine to 28.8% (22.9–35.2) with gemcitabine/capecitabine. Similar to previous trials, patients with R0 resections had better survival and significant benefit from combination treatment whereas the survival benefit for margin positive tumours did not reach significance.

The panel unanimously (100%) voted for the use of adjuvant chemotherapy (CTx) after R0 resection, with no role for simultaneous RCTx or sequential CTx/RCTx. Gemcitabine was chosen as preferred CTx regimen (73%), with minority votes for the use of 5-FU/leucovorin, FOLFIRINOX or gemcitabine/Nab-paclitaxel. The same holds true after R1 resection (80% were in favour of CTx). Please note, that this vote most likely would have been influenced by the positive results of the ESPAC-4 trial cited above which are in favour of the combination of gemcitabine and the orally active 5-FU derivative capecitabine [32] but had not yet been available during the conference. Also, whereas gemcitabine, 5-FU and gemcitabine/capecitabine have all been successfully investigated as adjuvant treatment in phase III trials, studies with other regimens (i.e. FOLFIRINOX and gemcitabine/Nab-paclitaxel) are still ongoing and results are pending. There is currently no role for biologically targeted or biomarker-oriented therapy in the adjuvant setting [33]. Even though preliminary reports have suggested that expression of the drug-transporter, hENT1 may be predictive for the benefit of gemcitabine-based CTx [34], technical problems with the commercially available antibodies preclude their use in clinical practice.

A major confounding factor is the rate and definition of R0 resection, which has a large impact on prognosis [35–38]. Whereas a clearly significant benefit of adjuvant CTx after R0 resection has been shown in subgroup analyses for overall survival with hazard ratios of 0.59 (standard deviation (SD): 0.11 with 5-FU), 0.76 (95% CI of 0.60–0.98 with gemcitabine) and 0.68 (95% CI 0.49–0.93 with gemcitabine/capecitabine) in the three largest trials, the benefit of postoperative therapy is more controversial after a R1 resection with hazard ratios of 0.99, 0.66 (95% CI of 0.39–1.13) and 0.90 (95% CI 0.72–1.13), respectively [4,31,32,36].

Two competing definitions of R0/R1 are currently used [38]. The International Union Against Cancer (UICC) distinguishes microscopically negative resection margins (R0) from 'the presence of residual tumour after treatment' (R1) which is usually defined as one or more tumour cells on the immediate resection margin (0 mm rule). In contrast, the British Royal College of Pathology (RCPath) defines R1 as the presence of tumour cells within 1 mm of the resection margin which leads to a 1.3–1.8 fold higher rate of resections classified as R1 [39,40]. The rate of R1 resections increases even further if all margins of the resected specimen are systematically stained, axially sliced and thoroughly investigated [37,41], a technique which is only inconsistently followed in clinical practice [42]. In a recent meta-analysis, R1 resection rates were 28% if a 0-mm margin rule was used, 51% with any slicing technique and a 1 mm-margin minimum, and 71% with an axial slicing technique and a 1 mm-margin minimum [37]. Five-year survival rates for 'R0' resected patients accordingly increase from 20.4% to 30.1% and 37.7% [38].

Most panel members suggested using the RCPath criteria for the definition of the R0 resection status (77%), with 89% requesting multicolour staining of the resection margins by the surgeon [40]. A practical suggestion is that any pathology report should clearly indicate the definition and give both versions: R1 according to UICC (i.e. *R1-direct* with a minimum margin of 0 mm), and R1 according to RCPath (i.e. *R1 < 1 mm* with a margin of 1 mm). If reporting only one, each study must state which definition is being used.

6. Neoadjuvant treatment in resectable or BR tumours

Neoadjuvant CTx and/or RCTx have the potential to improve surgical outcome. Several small phase II trials have suggested increased R0 resection rates and a promising effect on overall survival with multimodal therapy. The heterogeneity of trials limits the power of any conclusion [8], but two meta-analyses and a recent propensity score matched analysis of the US National Cancer Database suggested positive effects not only in BR tumours where secondary resection after downsizing might be an option but also in those tumours that appear to be resectable upfront [43–45].

When asked if patients with resectable tumours should receive neoadjuvant treatment, none of the panel members were in favour of this approach with all proceeding directly to resection. Several randomised trials which address this question have recently started accrual (e.g. AIO—NCT02047513; Alliance for Clinical Trials in Oncology—NCT02839343, UNICANCER—NCT02959879, NCT01900327, NCT02172976).

The general concept of 'borderline-resectable' tumours to highlight the potential for preoperative therapy was accepted by a majority (62%, with a number of abstentions) of the panel.

The most widely propagated definition of BR is provided by the National Comprehensive Cancer Network (NCCN) guidelines [7] which have also been adopted in Europe [8]. Briefly, any direct contact of the tumour with major arterial vessels but with less than 180° encasement or obvious involvement of the superior mesenteric or portal vein (for details see Table 2) is considered as BR. In contrast, major (>180°) involvement of the arteries or unreconstructible venous involvement is classified as unresectable LAPC. Even though this definition was judged as acceptable by a majority of voting panel members (50% abstentions; of the remaining panellists, 60% were in favour), most panellists would not consider the tumour to be classified as BR if there was only venous involvement (88% of those voting) and also were not decided as to its value for arterial involvement (50/50). In summary, the vast majority did not consider the NCCN definition to be the optimal discriminator for preoperative therapy. The main reason for this ambiguity was the potential discrepancy between technical feasibility and oncologic reasoning. Most of the panellists consider vessel involvement as a technical hurdle which primarily impacts surgical morbidity (75%), whereas the general concept of BR was felt to be oriented towards the improvement of oncological outcome (78%) through identification of a subgroup of patients who are in need of additional treatment.

If neoadjuvant treatment is considered as an option, chemotherapy (79%) with FOLFIRINOX (100%) was preferred. Alternatively, induction chemotherapy followed by RCTx was the favoured approach for 21% of the panel members. Ideally RTx should be intensity modulated (73%) with a fluoropyrimidine (100%) added as a radiosensitizer. In any case, a pathological diagnosis was considered mandatory before the start of multimodal treatment for 92% of panel members. If this was not possible, 88% would proceed directly to surgical exploration and omit preoperative therapy.

Table 2
Criteria defining resectability status according to the NCCN Guidelines (Version 2.2016) and Evans *et al.* (Ann Surg Oncol 2015).

Resectability status	Resectable	Borderline-resectable	LARC type A (may be considered for resection after neoadjuvant Tx)	LARC type B (not considered for resection)
Vessels defining resectability status				
Arterial				
CA	No s.t.c.	s.t.c. ≤ 180° or s.t.c. > 180° w/o involvement of aorta and GDA	s.t.c. > 180° amenable to resection, w/o involvement of aorta	s.t.c. > 180° with involvement of the aorta
SMA	No s.t.c.	s.t.c. ≤ 180°	s.t.c. > 180° but ≤270°	s.t.c. > 270° or 1st jejunal branch
CHA	No s.t.c.	s.t.c. w/o extension to CA or HA bifurcation	s.t.c > 180° with extention to CA amenable to reconstruction	>180° with extension beyond Bifurcation of proper HA
Venous				
SMV/PV	No s.t.c. or ≤180° w/o contour irregularity	s.t.c. ≤ 180° with contour irreg. or s.t.c. > 180°		Unreconstructable or s.t.c. with most proximal jejunal branch
IVC	No s.t.c.	s.t.c.		

CA, coeliac artery; CHA, common hepatic artery; GDA, gastroduodenal artery; HA, hepatic artery; IVC, inferior vena cava; LARC, locally advances rectal cancer; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein; s.t.c, solid tumour contact.

Restaging after preoperative treatment should include CT and/or MRI (54% CT, 8% MRI and 31% both) for optimal treatment planning, knowing that assessment of the treatment response by imaging is notoriously difficult in this patient population [6]. Serial measurements of CA 19-9 may be used to exclude progression but this has never been validated prospectively [46–48]. Therefore, all such patients without progression on radiologic imaging should undergo either exploratory laparotomy (57%) or at least restaging laparoscopy with the option for open surgical exploration if deemed appropriate (additional 43%).

7. Locally advanced disease

Patients with unresectable localised tumours without distant metastases (LAPC) are commonly considered as incurable. Systemic chemotherapy is widely used with a palliative treatment goal. If patients present with stable disease after 6 months of CTx, sequential RCTx is sometimes considered an option [12], with the aim to increase local control [10]. The addition of radiation therapy to chemotherapy, however is not supported by a recent European phase III trial, which did not demonstrate any overall survival benefit [49].

Of note, CTx as well as CRTx occasionally result in objective or even complete responses in individual patients which may render the tumour resectable [10,50,51]. In a recent patient-level meta-analysis, the pooled resectability rate after CTx for LAPC was 28% after FOLFIRINOX with R0 resections reported in 74% of the patients. There appears to be a subgroup of patients who—when responsive to systemic therapy—may technically be considered for resection. A first definition of this group was recently proposed by Evans *et al.* [10], again based on cross-sectional imaging at the time of diagnosis and the extent of vessel involvement (Table 2). The resulting concept separates BR tumours (which are technically resectable but might profit from additional neoadjuvant treatment to improve oncologic outcome) from a group of LAPC which are technically unresectable upfront but may become 'potentially resectable after response' (i.e. LAPC A according to Evans *et al.*) and from another group which will not be resectable (LAPC B).

The distinction of LAPC A from BR was considered useful by all panel members. Their recommendations for the primary approach matched those for BR tumours. CTx (67%) was the preferred option (CRTx suggested by 8%, sequential CTx-CRTx by 25%). Surgical exploration was recommended in all patients with response (100%) but also in patients with stable disease (58%).

8. Conclusion

In conclusion, standardised cross-sectional imaging was considered mandatory for any treatment decision. Based on vessel involvement, the panel distinguished four groups of patients with different treatment strategies. Those with a potential for primary R0 resection have to be separated from patients with either BR tumours—where resection is technically feasible but more likely to yield R1 resections—and from two groups of locally advanced tumours (LAPC) which include either patients might become technically resectable after downsizing (LAPC type A) or those who are definitely inoperable (LAPC type B). In clinical practice, the first group (resectable) would be directly referred to surgery, followed by postoperative CTx to improve overall survival. Neoadjuvant therapy clearly has the potential to further improve long-term results, especially in BR tumours, even though there currently is no evidence-based role for a combined approach outside of a clinical trial.

Addendum

For additional information, including site live lectures and discussions, please refer to: www.oncoconferences.ch/gicc16.

http://web.oncoletter.ch/kongressberichte-live-webcasts/id-3rd-gastrointestinal-cancer-conference.html.

Conflict of interest statement

There are no relevant conflicts of interest.

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