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Original Article

ESTRO ACROP guidelines for target volume definition in pancreatic cancer

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ABSTRACT

Despite of the predominant role of chemotherapy and surgery in pancreatic ductal adenocarcinoma (PDAC), radiotherapy (RT) still has a place in multimodal management of this disease where local tumour sequelae are fatal in about 40% of the patients. RT (chemoradiotherapy and stereotactic body radiotherapy) is used and investigated in the non-metastatic setting as part of definitive treatment strategies, in (neo)adjuvant settings and for locally recurrent disease. The ACROP committee was delegated by ESTRO to recommend target volume delineation for these clinical situations. The guidelines of this document are a result of a structured evaluation of the best available evidence by a panel of international experts in the field. Guidance for treatment planning including diagnostic imaging is provided. Recommendations are given for GTV delineation. The role and the definition of CTV volumes are critically discussed. Aspects of motion management and patient positioning are taken into account for PTV definition. Furthermore, aspects of delineation of organs at risk and of dose constraints are described in both, standard and hypofractionated, settings. This guideline has the purpose to support standardised and optimised processes of RT treatment planning for both, clinical practice and prospective studies.

Pancreatic RT has been used in the neo-adjuvant and adjuvant setting, and for the management of locally advanced or recurrent pancreatic tumours. The techniques, target volume definitions and fractionation schemes vary considerably in the published literature, even for the same indication. The aim of this technical RT guideline is to provide clinicians with consensus recommendations for target volume delineation (including imaging and patient-set up) for the treatment of pancreatic cancer in different clinical situations according to the used technique. A writing committee consisting of six European radiation oncologists with specialisation and experience in GI cancers produced the guideline draft. The guidelines were further refined after being reviewed by a review committee consisting of three different European radiation oncologists specialized in GI cancers. All points issued by the review committee have been discussed and were refined in accordance with the writing committee after consensus has been reached. It must be noted that the primary focus of this guideline is to discuss the technical aspects of pancreatic RT. Discussing the evidence-base for RT indications and specific RT technique (e.g. CRT versus SBRT) was considered to be beyond the scope of this guidance.

Anatomy

The pancreas and its relationship to surrounding structures

The pancreas is situated retroperitoneally extending from the duodenum (pancreatic head) to the splenic hilum (pancreatic tail).

The head of the pancreas lies in the loop of the duodenum, as it exits the stomach. The tail of the pancreas lies near the splenic hilum. Two key structures are traversing the pancreatic head, the common hepatic duct and the excretory pancreatic main duct

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(Wirsung), additionally (if present) the accessory duct (Santorini) all of which enter into the descending duodenum. The body is located dorsal of the stomach.

The neck of the pancreas is intercalated by the superior mesenteric artery (SMA) and vein (SMV). The pancreatic tail is found in close proximity to the splenic hilum where the splenic vein originates, which runs along the backside of the pancreatic tail and body until it finally forms the confluence of the portal vein (PV) dorsally of the pancreatic head by converging with the SMV. The pancreas superimposes the large retroperitoneal vessels, in particular the inferior vena cava (IVC), the abdominal Aorta (Ao) and the renal vessels. Superiorly of the pancreas the celiac axis (CA) leaves the Aorta dividing into the common hepatic artery (CHA), the right gastric artery and the splenic artery (SA), which runs along the superior edge of the pancreatic body and tail to the splenic hilum.

Anatomy of lymphatics in the upper abdominal region is complex and subject to considerable variation [1]. Aside from the anatomical description [2], two clinical classifications of lymph node regions are commonly in use: the UICC classification (currently in its 8th version) [3] and the Japanese classification [4–5]. For the purpose of this guideline, the expert panel agreed to use the Japanese classification (Table 1) because it is frequently used in most of the participating countries. The other classifications and a comparison of the described lymph node regions are available in the supplementary material. Contouring guidelines for the different regions of the Japanese classification are currently developed by ESTRO and will soon be published.

Pattern of lymph node involvement

Many patients with locoregionally confirmed pancreatic cancer suffer already from lymph node metastases. Several studies have examined the pattern of nodal metastases in surgically resected patients [6–13]. If elective nodal irradiation is considered, the regions with the highest risk of involvement should be considered to be included. The panel therefore made a corresponding recommendation based on the localization of the primary tumour in the target volume definition section. For detailed information regarding the results of the mentioned studies including a comparison, see supplementary section.

Pattern of recurrence after surgery

The distribution of local and nodal recurrences after curative resection of pancreatic cancer plays a major role in defining possible target volumes, not only for adjuvant but also for neoadjuvant strategies. Several studies have examined the region of highest risk [14–16] and found similar results although using different descriptions. Heye et al. found the largest percentage of local recurrences in the tissue around the SMA and an area defined by the CA/SMA (medial border), PV (anterior) and ICV (lateral) [14]. Lower but also considerable rates were detected at the resection margin of the residual pancreatic parenchyma and around the common/proper hepatic artery. Lymph node recurrences were mainly observed in the mesenteric root in close proximity to the SMA and left-laterally of the aorta. Dholakia et al. described most recurrences in close proximity either to the SMA (69%) or the CA (31%) [15]. In summary, most local recurrences occur in an area around the SMA/CA while lymph node recurrences are mainly found in the mesenteric root and the paraaortic space. Dholakia et al. and Yu et al. have reported specific recommendations how to cover these regions with a certain probability, for detailed information see supplementary material [15–16].

Diagnostic imaging

Proper diagnostic imaging is essential for accurate treatment planning. Currently, MDCT is the primary modality for detection and staging [17]. MRI offers similar sensitivity and specificity rates for detection, assessment of vascular involvement and prediction of resectability [17–18] but is the most sensitive imaging modality for the detection of liver metastases [19]. FDG-PET/CT is regarded as an optional additional imaging modality in most European countries except for the UK where the NICE criteria recommend it as a standard for all non-stage IV patients prior to therapy [20]. For detailed information regarding the value of different imaging modalities in diagnostic and planning see supplementary material.

Radiotherapy techniques

Conventionally fractionated CRT (25–30fractions), moderately hypofractionated (12–15 fractions) and Stereotactic Body Radiotherapy (SBRT) (3–12 fractions) are treatment options in the management of pancreatic cancer [21]. There is no data to confirm superiority of one approach over the other and detailed review of the pros and cons of either modality is outside the scope of this guideline, which aims to focus on the technical aspects.

Radiotherapy planning

Immobilisation and CT simulation

For planning purposes a dedicated contrast enhanced pancreatic CT protocol in treatment position is mandatory. Patients should be immobilized in treatment position with the immobiliza-

Table 1
Japanese classification used in this guideline and description of nodal areas.

Japanese classification	abb.	Description (simplified)
infrapyloric	6	along the first branch and proximal part of the right gastroepiploic artery down to the confluent of the right gastroepiploic vein and the anterior superior pancreaticoduodenal vein
common hepatic	8	located around the CHA
celiac	9	located around the CA
splenic hilar	10	located in the splenic hilum (along the splenic artery, distal to the pancreatic tail)
splenic artery	11	located around the splenic artery (superiorly to the pancreatic body/tail)
hepatoduodenal	12	located around the CBD, PV and proper hepatic artery in the hepatoduodenal ligament (upper border: branch of cystic duct)
post. pancreatoduodenal	13	located dorsally of the pancreatic head
SMA	14	located around the SMA
paraaortic	16	located around the aorta from CA to the inferior mesenteric artery, including nodes between aorta and ICV
ant. pancreatoduodenal	17	located ventrally of the pancreatic heads
subpancreatic	18	located inferiorly of the pancreas

abb.: abbreviation, CHA: common hepatic artery, CA: celiac axis, CBD: common bile duct, PV: portal vein, ICV: inferior caval vein

tion device depending on the intended treatment technique (conventionally fractioned RT vs SBRT). For conventionally fractionated RT, the patient should be positioned supine on a flat table top with the arms above the head, resting on a support (for example an alpha-cradle or similar ad hoc devices). Additionally a knee and/or foot support should be used. For SBRT a dedicated immobilization device should be employed for high precision positioning which may include abdominal compression. Fasting > 2 hours before planning CT is recommended to ensure smaller variations in organ fillings. The use of oral contrast (usually consisting of water with or without a small amount of oral contrast given before CT acquisition) is recommended especially for SBRT treatments because it allows an improved differentiation between pancreas and stomach/duodenum. Planning CT should be performed in exhalation breath hold with intravenous contrast at least in the pancreatic phase as explained above to define the GTV. Additional scans in the portal venous phase may be used to allow an easier identification of vascular structures especially if elective nodal irradiation is planned. It is strongly recommended to use body weight adapted volumes of contrast agents and bolus tracking for adequate separation of phases [22]. Triple-phased protocols (arterial, pancreatic, portal-venous phase) are recommended. These will require a minimum flow of 3 ml/s and delays of roughly 25, 40 and 70 seconds from injection without bolus tracking. If used, the bolus tracking ROI should be placed in the descending aorta. Typical delays will be roughly 5, 20 and 50 seconds from the tracking signal (usually 80–100 HU) as reviewed in Lee et al. [22]. The team should liaise with the local radiology department to define the local protocol appropriate for their equipment. Reconstruction should use a slice thickness 3 mm or less.

Motion assessment and management

Four-dimensional CT

Individual motion detection and consideration during treatment planning is mandatory due to large variations in pancreatic movement [23]. Four-dimensional CT (4D-CT) is currently the preferred method. This technique has the advantages to be easily implemented, not to require active cooperation of the patient and that the equipment is readily available for modern CT scanners. Nevertheless, there is some evidence that baseline 4D-CT may not always allow adequate prediction of pancreatic tumour motion over the course of treatment [24–25]. Most centres perform 4D-CT without contrast-enhancement or directly after contrast-enhanced 3D-CT for treatment planning for practical reasons. 4D-CT phases are usually matched rigidly to 3D-CT bony landmarks for ITV-construction (if an ITV approach is chosen), while the final treatment planning is done on the 3D-planning CT. Choi et al. recently reported that a dedicated contrast-enhanced 4D-CT protocol might be beneficial compared to the former approach [26].

Cine MRI in treatment position is an alternative to 4DCT with the advantage of better soft tissue contrast and specific scanning protocols can be obtained from the respective MRI manufacturer. Such protocols are also of specific interest for centres providing of an MR-LINAC.

Several motion management options exist for SBRT. A number of approaches are possible which are implemented in routine practice: In the absence of prospective comparisons, no recommendation can be made which method should be preferred.

- Continuous irradiation in free breathing using
  - o Internal target volume concept (ITV) based on CT scans in end breathing phases, 4D CT or cine MRI, time-averaged mid-position CT, or 4D PET/CT [27–30]
- Irradiation in specific breathing phases [31]
  - o Gating
  - o Active breathing coordinator (ABC system) [32–33]
  - o Real-time tumour tracking

Target volume delineation

Summary

Target volume definition requires adequate identification of the primary tumour (including possible infiltration of adjacent structures or organs), involved regional lymph nodes, possible regions of increased risk for subclinical disease (for example elective nodal regions) and information about tumour motion. Currently, contrast-enhanced multi-detector computed tomography (CE-MDCT) is the single most important imaging tool for target delineation. In general, any available information from pre-treatment imaging should be taken into account for target volume definition, although direct fusion of diagnostic images not taken in treatment planning position is not recommended. For respiratory motion assessment four-dimensional CT (4D-CT) is the most important imaging tool, however useful additional information can be obtained for example by ultrasound (US), cine mode MRI or 4D-PET/CT [34–36]. Image-guided RT needs to be planned prior to the planning CT. IGRT aspects need to be considered even more stringently for patients who are planned to be treated with SBRT. Fiducial marker implantation may be necessary if no other reliable structures for IGRT are available (e.g. surgical clips) or if the quality of the IGRT imaging method does not allow sufficient matching of the target region. This is the case for patients treated with CybeKnife™ or when on board imaging provides insufficient soft tissue contrast

Defining the gross tumour volume (GTV) (all indications except adjuvant)

The GTV is delineated in the pancreatic phase planning CT. This is defined as the primary pancreatic tumour and radiologically enlarged lymph nodes (defined as short axis diameter $\geq$ 1 cm, or PET positive). All available diagnostic imaging should be taken into account (e.g. diagnostic CT, MRI or FDG-PET/CT). MRI is especially helpful for outlining of tumour, but also for the position of bowel structures that are typically very close to the tumour and for motion imaging [37]. If induction chemotherapy was performed prior to neoadjuvant RT, baseline imaging should also be reviewed, although GTV definition should be based on actual imaging.

Large inter-observer variation is a recognized problem with pancreatic cancer RT [38–39]. For planning purposes it has recently been show that even the addition of MRI to CT and 4D-CT without image fusion improved GTV delineation and resulted in smaller interobserver variation and smaller GTV volumes [40]. Practical recommendations for MRI based treatment planning have been recently published by Heerkens et al. [41]: Briefly, MRI (1.5–3.0 T, slice thickness $\leq$ 3 mm) should be performed on the same day as the planning CT with reproducible organ-filling, minimized differences in patient positioning and in the same respiration phase. GTV should be delineated on T1-weighted images with and without contrast-enhancement.

Defining the internal target volume (ITV) (all indications except adjuvant)

The internal target volume (ITV) is created from the available 4D-CT scan by contouring the tumour on multiple phases of respiration. A common practice is to outline the tumour on the 3D planning scan and on the maximum inhale and maximum exhale components of the 4D CT – the contours are fused to form the ITV. The ITV is then adjusted by running the 4D cine, to ensure that

it encompasses the tumour on all phases of respiration. One of the problems of 4D-CT is that pancreatic tumours might not be visualized because of the dependence on the correct IV contrast phase. There are several solutions to this problem: the use of IV contrasted 4D CT [26] may be helpful in improving image quality. In addition, if fiducial markers have been placed, the motion of fiducial markers at close proximity to the GTV can be measured and extrapolated for the expansion of the GTV to create an ITV. Alternatively, 4D-FDG-PET/CT can be employed. Cine-MR is another alternative, and can be used to obtain an ITV. Usually, the GTV or the ITV, if used, also defines the CTV without an additional margin. Typical SBRT PTV definition does not use additional CTV margins on top of the ITV. Abdominal compression can significantly reduce respiratory motion to $\leq$ 5 mm in all directions and thus the size of the ITV but abdominal compression does still require quantification of motion and usually employment of an ITV. Centres which perform gating or tracking do not require an ITV.

Defining the clinical target volume (CTV)

General considerations for CTV in primary tumours and pathological lymph nodes

The CTV as defined originally by ICRU report 50 in 1993 is the volume where radiologically there is no visible tumour, where however there is a high likelihood of microscopic tumour spread. For pancreatic cancer primary tumours the discrepancy of CTV volumes with pathological volumes was analysed in two studies [42–43]. Since these studies are of high relevance in the context of the topic of this report a closer look at the results is justified. Qiu and co-workers evaluated this discrepancy in 63 patients with preoperative CT from a 64 line MDCT with reconstruction at 0.75 mm slice thickness at 0.5-mm intervals and pathohistology. Radiologists measured maximum tumour dimension on dual phase IV contrast conventional CT (C-CT) scans and after 3D volume rendering (3D-CT). Tumours were staged T3 and located in the pancreatic head in two thirds, respectively, with a median pathologic size of 3 cm. Tumours < 3.0 cm were underestimated both, with C-CT maximum tumour diameter (MTD) and 3D-CT (median 6.5 mm, p = 0.003 and 2.0 mm, p = 0.023, respectively). This is relevant for radiotherapy in the neoadjuvant setting and for definitive therapy. On the other hand, tumours with pathologic MTD < 3.0 cm had a trend to be overestimated on C-CT by a median of 2.5 mm (p = 0.08) and on 3D-CT by 4.2 mm (p = 0.002) compared to pathology which is of interest for adjuvant radiotherapy. The influence of tumour location was also investigated. Tumours in the pancreatic head were underestimated by a median of 2.0 mm on C-CT compared to pathology (p = 0.015), while tumours located elsewhere in the gland were not. In a second study 97 patients also with predominantly pancreatic head/uncinate/neck tumours (71%) were scanned with C-CT, but not with 3D-CT [43]. Median MTD was 25 mm on CT versus 34 mm pathologically (p < 0.0001). Tumour size was underestimated by a median of 7 mm on C-CT compared to pathology. The range of the discrepancy was −15 to +43 mm and as in the study by Qiu et al., larger tumours were less discrepant compared to smaller tumours [42]. Overall in 84% the tumour was larger on pathology as on C-CT. Duodenal infiltration at pathology was commonly missed on C-CT [43].

In summary, tumours larger than 3 cm appear to be safely treated without a designated CTV whereas for tumours <3 cm a GTV to CTV expansion should at least be considered, especially when located in the pancreatic head. Arvold et al. developed a formula to calculate an appropriate CTV margin to cover 97.5% of cases based on tumour diameter on CT [43]. The formula is based on a single report including a low number of patients resulting in large confidence intervals. Furthermore, the authors addressed the problem of adequate orientation of the pathological specimen as a limitation of their study. Therefore the use of this formula especially for SBRT cases cannot be generally recommended. Free-breathing SBRT concepts using an ITV are often assumed to comprise already sufficient margins to be regarded as a surrogate for CTV despite of the lack of evidence for this practice [44]. For non-free breathing tumour volume definition we recommend to consider CTV margins that take into account the discrepancies described above. This applies to all clinical situations except for adjuvant treatment for radiotherapy of the primary tumour. Posterior margins between the pancreas and the aorta as well as vena cava inferior are not described well enough in the literature to be recommended [44–45]. An exception might be locally recurrent cancer where the group from Johns Hopkins University systematically analysed high risk volume for recurrence [15]. Nevertheless, this approach has not been systematically tested in clinical practice.

Compared to primary tumours, even weaker evidence is available for the definition of a CTV for pathologic nodes (>1 cm in the short axis) from radiology to pathology comparisons. For lymphatic nodes the discrepancy between radiology and pathology is not so much size but rather between detection rates: Masuda and colleagues have described a detection rate of 31% at imaging (CT, MRI or EUS) compared to a rate of 59% of pN + after primary resection in 490 patients with PDAC [46]. Radiologically positive nodes contain also false negatives and vice versa. Additionally, Prenzel et al. showed that LN size in resected specimens is not an accurate predictor of pathologic involvement [47]. In pancreatic cancer FDG-PET/CT was not found to increase the detection of positive nodes [48]. In gastric cancer, Park et al. have expanded the nodal GTV by 1.5–2.5 cm in all directions, which is larger as CTV margins for the GTV of the primary tumour and therefore is not recommended [49]. Treating nodal relapse in pancreatic cancer after resection with a 3 mm CTV resulted in 12 and 24 months local control rates of 84% and 62% in a small retrospective analysis [50]. In summary, the use of a GTV to CTV expansion for lymph nodes cannot be generally recommended. If considered, small margins seem to be sufficient based on the limited data. Contouring guidelines for the different regions of the Japanese classification are currently developed by ESTRO and a manuscript is in preparation.

Macroscopic tumour in Neo-adjuvant chemoradiotherapy

In patients who underwent induction chemotherapy, creation of an additional CTV that consists in the ex-GTV prior to the start of induction chemotherapy may be considered. This approach is currently employed in a prospective trial of chemoradiotherapy (CONKO-007, EudraCT-Nr: 2009–014476-21) but to date there is no prospective evidence for this approach, i.e. both techniques with and without inclusion of the initial tumour volume are adequate.

Elective nodal CTV

Indication for elective nodal irradiation

Inclusion of elective nodal volumes is a key element in adjuvant radiotherapy. However, in patients without resection there are two philosophies, one with and one without elective nodal irradiation (ENI). The philosophy without ENI has three main reasons: [1] large volumes as a result of ENI have resulted in significant toxicities and consequently also led to reduced doses of chemotherapy [51–53]. (2) the use of higher doses of radiotherapy (>$EQD2_{10}$ 50 Gy) was shown to be safe in studies restricting volumes to GTV and margins [54–55]. (3) Recurrences at lymph nodes are rare according to the available evidence [54,56]. Based on these reasons

ENI is not recommended in patients receiving CRT or SBRT for LAPC.

Neoadjuvant radiotherapy in its proper sense is restricted to patients with resectable pancreatic cancer and with BRPC and does exclude patients with LAPC. In this situation a part of the chemoradiotherapy studies of the last decade define the target volume as the GTV with margins (CONKO-007; **EUDRACT** 2009–014476-21). Other studies of the same era define specific nodal areas for inclusion into ENI [57–59]. The rationale for ENI in this situation is similar to that in adjuvant CRT (see below). For patients with BRPC, i.e. with tumour contact to regional major arteries (CT, SMA), the recommendation of ENI is weak, whereas for patients with resectable tumours it is moderate. Vascularly defined nodal regions that are typically contained comprise the celiac trunk, the superior mesenteric artery, hepatic artery, superior mesenteric vein and portal vein [7,13,15]. If ENI is used for target volume definition then this is recommended to be done in analogy with postoperative ENI definitions as discussed below [57,59–60].

Due to the higher probability of local control at the primary tumour after resection, the value of regional control gains of importance in the neoadjuvant context similar to adjuvant treatment. There is also a circumscribed high frequency of local relapses after resection in defined lymphatic regions as mapped in a recent analysis in proximity to the celiac trunk and the superior mesenteric artery [15]. Importantly, these sites of frequent relapse match well with the dorsal regions where the degree of radicality of the lymphatic dissection is limited to avoid postoperative morbidity.

Selection of elective nodal areas and definition of the CTV

If elective nodal volume is treated, based on patterns of nodal involvement (see above), we recommend inclusion of the following nodal regions:

For pancreatic head tumours: common hepatic nodes, the celiac nodes, the hepatoduodenal nodes, the anterior and posterior pancreaticoduodenal nodes, the superior mesenteric nodes, the paraaortic nodes from the celiac trunk to the lower border of the left renal vein (JPS 16a2) and the superior and inferior head nodes. The respective numbers of the Japanese classification are given in Table 1.

Body and tail tumours: common hepatic nodes, the celiac nodes, the hepatoduodenal nodes, the superior mesenteric nodes, the paraaortic nodes (JPS 16a2), the subpancreatic nodes and the splenic artery

Generally, for contouring of elective volumes, the practical approach is to contour first the respective vessel defining the nodal area to be treated. Next, the vessel is expanded isotropically by defined value as described by several authors who have provided guidance regarding elective nodal definition in the abdomen: Kalbasi and Ben-Josef and Brunner et al., which was used in two prospective randomized neoadjuvant trials [7,61] (ISRCTN78805636 - NCT00335543; EudraCT Number 2012–003669-17). Based on the recurrence pattern after surgery (see above), independently of the primary tumour location the region around the CA/SMA should be included according to Dholakia et al. with a 2–3 cm margin right-laterally and a 1–2 cm margin in all other directions [15]. Special attention should be paid to cover the region between CA/SMA (medially), PV (anteriorly) and ICV (laterally). Delineation of the major vessels (especially most proximal 1–2 cm of celiac trunk, most proximal 2–3 cm of the SMA, portal vein from confluence to bifurcation, the aorta from celiac trunk to renal artery) is recommended. As mentioned above a manuscript on the subject of the different regions of the Japanese classification is in preparation by ESTRO.

Locally advanced pancreatic cancer:

In locally advanced pancreatic cancer ENI is not recommended. Yamazaki et al. have not identified any regional lymph node failure with full dose gemcitabine with limited field RT [62]. Moreover, CRT is commonly delivered after a course of induction chemotherapy, often FOLFIRINOX or gemcitabine doublets, which may be adequate in controlling micrometastatic disease in regional nodes. Recent trials of long-course CRT in the definitive setting have omitted ENI [63–64].

For patients receiving SBRT, additional expansion of the ITV is not usually applied to take CTV into account. In the case of a pathological lymph node, several subgroups also do not use an expansion of the GTV to create a CTV.

Adjuvant chemoradiotherapy:

Contouring of the target volume starts with the creation of the regions of interest as given in Table 2a [60]. To create the overall CTV, merge all the sub volumes of Table 2b and add this volume to exclude overlaps with normal organs. For creation of the PTV proceed as described below.

Defining the planning target volume (PTV)

The PTV is the required margin to compensate for set-up errors and therefore it is dependent on the consistency of the positioning. Each unit of radiotherapy has to quantify their set-up errors for the upper abdomen as a function of the used positioning method.

Neo-adjuvant chemoradiotherapy

The ITV of the primary tumour is isotropically expanded to define the PTV of the primary tumour according to the setup inaccuracy measured by the respective institute (usually 5–10 mm). If no 4D-CT and no gating/tracking is used, an expansion of at least 2 cm in the superior-inferior direction and 1.5 cm in all other directions seems advisable [63].

Locally advanced pancreatic cancer (LAPC) and recurrent tumours

A PTV including the ITV with a 5–10 mm circumferential margin is recommended when 4D-CT is available. In the absence of

Table 2a
Regions of interest for adjuvant chemoradiotherapy (RTOG consensus).

Region of interest (ROI)	Definition	Comments
Preoperative tumor volume	- include surgical clips for close margins - contour preoperative GTV after image fusion	-discuss significance of clips with surgeon
Celiac artery	Proximal 10–15 mm up to 1st branching	none
Superior mesenteric artery	Proximal 25–30 mm	none
Portal vein	From confluent to hilar bifurcation	none
Pancreaticojejunostomy	To the right from pancreatic remnant to junction with jejunum.	Do not include a pancreatogastrostomy
Aorta	Craniocaudal: from uppermost contour of all other structures to the bottom of vertebra L2*	none

Table 2b
The above defined ROIs will then be expanded to create clinical target volumes (CTVs).

ROI	Isotropical	Right - left	Ventral - dorsal	Cranial – caudal
Preoperative tumor volume	5–10 mm	n.a.	n.a.	n.a.
Celiac artery	10(−15)mm	n.a.	n.a.	n.a.
Superior mesenteric artery	10(−15)mm	n.a.	n.a.	n.a.
Portal vein	10(−15)mm	n.a.	n.a.	n.a.
Pancreaticojejunostomy	5–10 mm	n.a.	n.a.	n.a.
Aorta	n.a.	Rt: 25–30 mm Lt: 10 mm	Ant.: 20–25 mm Post: 2 mm	Top contour of all others Bottom of vertebra L2

Abbreviations: Ant. = anterior; Lt = left; n.a. = not applicable; Post. = posterior; Rt = right.

4D-CT, it is recommended that the PTV includes the GTV with a 1.5 cm margin in the anterior, posterior, and lateral directions and at least 2 cm margin in the cranial and caudal directions. However, 4D-CT is highly recommended to avoid gastrointestinal toxicity by restricting the volume.

SBRT: All ITV are further expanded by institutionally measured dimensions to obtain the PTV, usually 0–5 mm [65–67].

Adjuvant Chemoradiotherapy:

Summary of ITV, CTV, PTV expansion in Neo-adjuvant CRT, CRT for LAPC, SBRT

A summary of the target volume expansions is given in Table 3.

Defining the organs at risk (OAR) (all indications)

The following risk structures (OAR) should be delineated: stomach, duodenum, small bowel, spinal cord, left and right kidney separately as well as liver. Delineation of the OAR is recommended to follow the guidelines of Jabbour et al. and Goodman et al. [60,68]. When 4D-CT is available, stomach and duodenum internal risk volumes (IRV) near the PTV may be delineated in analogy to the ITV of the tumour , however this not standard [69]. Where MRI is available, GI tract is best seen on T2-weighted images but can be contoured also in T1 for registration purposes.

Special consideration for SBRT: For SBRT the dose constraints of the stomach, duodenum and jejunum are particularly critical. It is recommended to contour the stomach and the duodenum completely whereas all other parts of the bowel should be contoured at least at the level of the PTV. Bowel volume changes due to peristalsis cannot be accurately predicted but they should be taken into account at a later step during plan analysis. Several approaches to protect bowel structures are used. One of them is to decrease the PTV at the interface of the PTV with bowel PTVs individually, and another one is to create quantifiable overlap regions between OARs and the PTV that are protected by a simultaneous integrated boost (SIP) [70]. None of these techniques has prospective evidence but a prospective trial for the SIP approach is recruiting (DRKS00015816).

Radiotherapy technique

Intensity modulated RT (fixed fields or rotational = VMAT) is strongly recommended for chemo-radiotherapy. Even if 3D conformal RT is considered for CRT, it must be recognized that IMRT is better sparing of OARs [71–73].

Dose fractionation, dose constraints

Long course CRT

Long-course CRT is delivered in conventional fractionation or moderately hypofractionated with daily doses of 1.8 to 3.0 Gy. Duration of treatment is three to six weeks to total doses of 30–55 Gy [74]. Dose prescription is mandatory to follow the ICRU report 83. Most common schemes are 25–30 fractions x1.8 Gy [63–64] or 10-12x3 Gy [75].

Concurrent chemotherapy consists either in oral capecitabine, continuous infusional 5-fluorouracil or weekly gemcitabine. Capecitabine is the preferred radiosensitizer based on a single prospective trial which demonstrated superiority of capecitabine over

Table 3
Target volume expansions for adjuvant chemoradiotherapy.

	Neo-adjuvant CRT	CRT for LAPC/recurrent	SBRT
exGTV (primary CTV)	Tumour volume Consider CTV margin based on size and location	Tumour volume Consider CTV margin based on size and location	Tumour volume
ITV	Tumour volume (or primary CTV) encompassed in all phases of respiration	Tumour volume (or primary CTV) encompassed in all phases of respiration	Tumour volume encompassed in all phases of respiration
Elective nodal CTV	Optional, if used: Head: (see above) common hepatic nodes, the celiac nodes, the hepatoduodenal nodes, the anterior and posterior pancreaticoduodenal nodes, the superior mesenteric nodes, the paraaortic nodes and the superior and inferior head nodes Body and tail: common hepatic nodes, the celiac nodes, the hepatoduodenal nodes, the superior mesenteric nodes, the paraaortic nodes, the subpancreatic nodes and the splenic artery	No elective nodal CTV	No elective nodal CTV.
PTV	4D available: ITV + 0.5–1 cm 4D not available: GTV (or primary CTV) and elective nodal CTV (if used) + 1.5 cm (A-P, L); ≥2cm (CC)	4D available: ITV + 0.5–1 cm 4D not available: GTV (or primary CTV) + 1.5 cm (A-P, L); ≥2 cm (CC)	ITV + 0–5 mm

Table 4a
Dose constraints for long course chemoradiotherapy (for 1.8–2 Gy/fraction). Adapted from the NCCN Clinical Practice Guidelines. *adapted from RTOG 0936 and RTOG 1102. **adapted from RTOG 0848.

Organ at risk	Constraint
Duodenum	$D_{max} \leq 55$ Gy Circumferential* dose ≤ 50 Gy V50 $\leq$ 10 cc (optimal)V50 $\leq$ 10%, V45 $\leq$ 15%
Stomach	$D_{max} \leq 55$ Gy V45 $\leq$ 75 cc (optimal) V50 $\leq$ 10%, V45 $\leq$ 15%
Small bowel	$D_{max} \leq 55$ Gy V50 $\leq$ 10 cc (optimal) V15 $\leq$ 120 ccm (optimal) V50 $\leq$ 10%, V45 $\leq$ 15%
Liver	$D_{mean} \leq 25$ Gy
Kidney (summed right and left)	$D_{mean} \leq 18$ Gy V20 $\leq$ 32%
Spinal cord	D0.1 cc $\leq$ 45 Gy

*Circumferential dose means that the dose not only at the adjacent side of the hollow organ wall next to the PTV but also at the opposite aspect of the wall, i.e. the dose is applied to the entire circumference of a segment of the hollow organ. Adapted from QUANTEC, RTOG 0848, SCALOP-2, NCCN

gemcitabine [63]. All patients should be treated with proton pump inhibitors (PPI) during treatment and at least for 3 months thereafter.

Table 4a gives an overview of dose constraints for organs at risk (conventional fractionation).

SBRT

The majority of experienced centres use a minimum of five fractions, being the typical fraction number in North America, whereas in Europe up to 12 fractions are used [21] as a risk adapted fractionation strategy, i.e. the closer of the PTV is to stomach or duodenum, the higher is the number of fractions. The dose prescription should follow the ICRU 91 for SBRT prescription principles [76].

Dose limiting OARs are first of all duodenum and stomach and SBRT has been reported to lead to high grade late complications in these organs. There is still some uncertainty about the dose constraints of these organs, however, a number of recent publications have provided more information. Other organs at risk are liver, kidney, spinal cord and colon. The current knowledge on SBRT constraints was recently summarized by Hanna et al. in a UK Consensus article [77]. Table 4b shows an overview of important constraints for 3 and 5 fractions for the mentioned organs at risk based on this publication. To reduce the risk of severe side effects to duodenum and stomach, prophylactic gastric acid reduction with PPI at therapeutic doses is recommended. Although there is no available evidence, many centres prescribe PPIs, such as pantoprazole at 2 × 40 mg per day for the first three months during SBRT and for the following 3 months with a subsequent dose reduction to 1 × 40 mg for a further 3–6 months depending on the dose to the stomach or duodenum and on patient history. Patients with a positive history of gastric or duodenal ulcer have a higher risk of toxicities and dose constraints may have to be individually adapted.

Treatment and IGRT

Daily pre-treatment volumetric IGRT with cone-beam technology is considered mandatory. Implanted markers are helpful to facilitate IGRT. Reproduce the fasting and oral contrast procedure as undertaken at planning. Daily oral pre-treatment contrast with a defined small volume and after at least two hours of fasting were described as techniques to increase consistency in stomach and bowel filling [78–79]. Intra-fraction patient or tumour position monitoring is not routinely required. However, if the treatment time is >15 min or non-coplanar fields are used there needs to be further imaging for SBRT.

Quality assurance (QA) is a necessary component of pancreatic SBRT. This comprises mechanical accuracy and dosimetric accuracy of median 3% at isocentre (2–5%) in a phantom in the treatment field. Further mandatory QA measures comprise dedicated small field dosimetry detectors for commissioning, end-to-end testing in a phantom, QA of in-room IGRT systems and of the 4D-CT

Table 4b
Dose constraints according to the UK recommendations [77] for stereotactic body radiotherapy using 3-or 5 fraction regimens.

Description	Constraint	3 fractions		5 fractions	
		Optimal	Mandatory	Optimal	Mandatory
Duodenum	DMax (0.5 cc)	–	<22.2 Gy	–	<35 Gy
	D1 cc	–	–	<33 Gy	–
	D5 cc	–	<16.5 Gy	<25 Gy	–
	D9 cc	–	–	<15 Gy	–
	D10 cc	–	<11.4 Gy	–	<25 Gy
Stomach	DMax (0.5 cc)	–	<22.2 Gy	<33 Gy	<35 Gy
	D5 cc	–	–	<25 Gy	–
	D10 cc	–	<16.5 Gy	–	<25 Gy
	D50 cc	–	–	<12 Gy	–
Small bowel	DMax (0.5 cc)	–	<25.2 Gy	<30 Gy	<35 Gy
	D5 cc	–	<17.7 Gy	<25 Gy	–
	D10 cc	–	–	–	<25 Gy
Large bowel	DMax (0.5 cc)	–	<28.2 Gy	–	<32 Gy
Liver	V10 Gy			<70%	
	mean dose			<13 Gy	<15.2 Gy
	D50%	<15 Gy			
	Dose to ≥ 700 ml	<15 Gy	<19.2 Gy		
Common bile duct	DMax (0.5 cc)	<50 Gy	–	<50 Gy	–
Kidneys (individual	Mean dose	–	–	<10 Gy	–
and combined)	Dose to ≥ 200 cc	–	<16 Gy	–	–
Kidney (solitary)	V10 Gy	–	–	<10%	<45%
Great vessels	Dmax (0.5 cc)		<45 Gy		<53 Gy

Dmax is the near point maximum dose, defined as D0.5 cc, which is the minimum dose to the 0.5 cc volume of the organ receiving the highest doses; D1 cc, D5 cc, D9 cc, D10 cc, D50 cc are the minimum doses to the specified volume of the organ that receive the highest doses; V10 Gy is the percentage volume of the organ receiving a dose of 10 Gy or higher; dose to ≥ 700 cc and ≥ 200 cc is the maximum dose to the specified volume of the organ that receives the lowest doses (adapted from Hanna GG et al. Clin Oncol 2018 [77].

scanner. QA of the mechanical accuracy of the delivery system should be performed in minimum weekly intervals and quality checks of alignment of the IGRT system with the MV treatment beam should be performed daily or at least weekly. If VMAT planning is used, quality assurance must be measured individually for each patient.

Follow-up

All patients should be followed-up regularly. Since many patients will have subsequent treatment, follow-up ideally is organised in an interdisciplinary structure integrating clinical follow-up, laboratory and imaging measures. Special aspects include gastrointestinal late effects and re-evaluation of secondary resection in borderline resectable and LAPC patients. Since response at imaging is often underestimated due to scar tissue which cannot reliably be distinguished from tumour, multidisciplinary boards should consider surgical exploration to answer the question of resectability provided that complete re-staging shows no signs of distant metastasis and that the general condition of the patient is good. An analysis of the interval between CRT and resection in relation to pathologic response showed that patients with an interval of $\geq$11 weeks compared to a shorter interval were significantly more likely to experience a major response [80]. We therefore recommend reconsidering resection also after intervals of $\geq$3 months with the consideration of further systemic therapy after completion of radiotherapy. Re-staging may be performed as early as 5–6 weeks after completion of therapy [57,59]. Lastly we would like to recommend including patients with pancreatic cancer that receive radiotherapy in clinical trials.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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