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REVIEW

Chemoradiation for Ductal Pancreatic Carcinoma: Principles of Combining Chemotherapy with Radiation, Definition of Target Volume and Radiation Dose

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Summary

Review of the role of chemoradio-therapy in the treatment of locally advanced pancreatic cancer with a specific focus on the technical feasibility and the integration of chemoradiotherapy into multimodal treatment concepts.
Combined chemoradiotherapy of pancreatic cancer is a safe treatment with an acceptable profile of side effects when applied with modern planning and radiation techniques as well as considering tissue tolerance. Conventionally fractionated radiation regimens with total doses of 45-50 Gy and small-volume boost radiation with 5.4 Gy have found the greatest acceptance. Locoregional lymphatic drainage should be included in the planning of target volumes because the risk of tumor involvement and local or loco-regional recurrence is high. Up to now, 5-fluorouracil has been considered the "standard" agent for concurrent chemoradio-therapy. The role of gemcitabine given concurrently with radiation has not yet been defined, since high local efficacy may also be accompanied by enhanced toxicities. In addition, no dose or administration form has been determined to be “standard” up to now.
The focus of presently ongoing research is to define an effective and feasible regimen of concurrent chemoradiotherapy. While preliminary results indicate promising results using gemcitabine-based chemoradio-therapy, reliable data derived from mature phase III trials are greatly needed. Intensity-modulated radiotherapy has been developed to improve target-specific radiation and to reduce organ toxicity. Its clinical relevance still needs to be defined.

Introduction

Radiotherapy plays an important role in the treatment of non-metastatic pancreatic cancer [1, 2]. Due to the near absence of early symptoms and the late appearance of mostly uncharacteristic complaints, only about 20% of tumors are diagnosed at a surgically resectable stage [3]. Adjuvant chemoradio-therapy is applied to reduce the very high risk of local recurrence. Neo-adjuvant radio- or chemoradio-therapy aims to improve resectability [4]. A conclusive assessment of whether this will also improve the survival rate is not yet possible.
About 20-40% of patients present with a locally advanced tumor which is not curable by resection. The aim of primary radio-(chemo-)therapy in this situation is to achieve a local response with the aim of preventing

local tumor complications (e.g. pain, hemorrhage or stenoses of the choledochus or the duodenum) and perhaps achieving secondary resectability through downstaging or downsizing [5, 6].
Since pancreatic cancer appears to be a systemic disease early on, about 40-70% of patients already present with distant metastases at primary diagnosis. In this situation, radiotherapy can be applied for the local palliation of tumor complications such as hemorrhage or pain.
This review aims to provide an overall view of the technical administration of radiotherapy and explain how it can be included in multimodal therapy regimens.

Systemic Chemotherapy

There is no common agreement that locally advanced pancreatic cancer patients should either receive radiochemotherapy or chemotherapy alone. A retrospective cohort study performed on 1,696 patients with locally advanced pancreatic cancer, documented by means of surveillance, epidemiology, and end result medicare database indicated that only 44% of patients received some form of cancer-directed treatment. The risk of death was calculated with logistic regression depending on the administered therapy modality. The hazard ratio (HR) was the lowest when chemoradiotherapy was applied (HR: 0.44; 95%CI: 0.39-0.50) as opposed to radiation alone (HR: 0.68; 95% CI: 0.58-0.79) or chemotherapy alone (HR: 0.66; 95% CI: 0.54-0.81) [7].
With regard to systemic chemotherapy, the standard therapy was5-fluorouracil (5-FU) administered for an extended period. More aggressive combination therapies such as FAM (5-FU, adriamycin/doxorubicin, mitomycin C), SMF (streptozotocin, mitomycin C, 5-FU), or the Mallinson regimen (5-FU, cyclophosphamide, methotrexat, and vincristin) with increased toxicity, did not result in an improvement in survival time [8, 9]. Even newer agents, such as paclitaxel, docetaxel, irinotecan, topotecan or oxaliplatin, could not be established as an effective treatment for pancreatic cancer [10].
A modest improvement in treatment efficacy could only be shown after the introduction of the pyrimidine analogue gemcitabine [11], which is characterized not only by a positive effect on clinical benefit response but also by an acceptable risk of side effects. Gemcitabine is presently regarded as a standard medication in advanced pancreatic cancer. The combination of gemcitabine with cisplatin or 5-FU improved response rates and time to progression [12]. Preclinical data indicated that gemcitabine acts as an effective radiation sensitizing agent which thereby allowed its inclusion into simultaneous chemoradiotherapy protocols [13, 14].

Radiotherapy

Since pancreatic cancer is only moderately sensitive to radiation, doses of 70 Gy and higher are recommended for radiotherapy when given without chemotherapy [15]. However, the radiosensitivity of adjacent organs such as the liver, kidneys, stomach, and small intestine as well as the spinal cord, considerably limits the option of administering such doses percutaneously. A high rate of side effects and complications are to be expected. Furthermore, radiotherapy alone did not improve the overall survival rate [16].
Intraoperative radiation therapy (IORT) with fast electrons offers the opportunity of administering comparatively high radiation doses directly to the tumor or to the tumor bed, while protecting the adjacent organs at risk. With a moderate rate of side effects, IORT doses of 25-40 Gy can achieve local tumor- or pain-control [17, 18]. However, IORT alone did not improve the overall survival rate.
IORT can also be used as a boost in combination with external radio- (chemo-) therapy [19, 20, 21]. Thereby, it is possible to reduce the percutaneous radiation dose to 40-50 Gy while maintaining improved local

Table 1. Randomized phase III-studies of chemoradiotherapy of locally advanced unresectable pancreatic cancer.

Author	No. of Patients	Therapy	Median survival (months)	Comment
Mörtel, Mayo (1969) [16]	32	35-40 Gy	6.3	Significant
	32	35-40 Gy + 5-FU	10.4	
GITSG (1981) [26]	83	40 Gy split + 5-FU	9.6	Significant
	86	60 Gy split + 5-FU	9.2	
	25	60 Gy split	5.2	
GITSG (1988) [27]	24	54 Gy + Sq SMF	10.5	Significant
	24	SMF	8.0	
GITSG (1985) [57]	73	60 Gy split + 5-FU	8.4	Not significant
	72	60 Gy split + Adri	7.5	
Klaassen, ECOG (1985) [28]	47	40 Gy + 5-FU	8.3	Not significant
	44	5-FU	8.2	

Sq: sequential
Adri: adriamycin

tumor control. While a definite survival advantage has not been proven [22, 23], particularly high total doses of IORT (IORT 20.0 Gy, external beam radiation therapy (EBRT) up to 50.0 Gy), have induced considerable complications, specifically with regard to hemorrhage [24]. Other reasons against a more widespread use of IORT lie in the technical and logistical complexity of this procedure. In addition, there are radiobiological objections to be raised. Because of the interval of four to six weeks, which pass between IORT and external radiotherapy as a rule, accelerated repopulation may reduce the antitumor effect [25].

Concurrent Radiochemotherapy

In the 1960s, the Mayo Clinic had already documented the improved efficacy of combined chemoradiotherapy in a randomized study. This trial indicated an improved survival rate of 10.4 months in patients treated with 5-FU-based chemoradiotherapy (35 Gy in 4 weeks) as compared to 6.3 months observed in the group with radiotherapy only [16]. These results were confirmed in further randomized studies carried out in the 1980s by the Gastrointestinal Tumor Study Group (GITSG). In unresectable patients, radiotherapy (40.0 or 60.0 Gy) in combination with 5-FU resulted in a significantly improved survival rate (9.6 and 11.4 months, respectively) as compared to 5.2 months after radiotherapy only (60.0 Gy) [26]. A further GITSG study demonstrated a significantly longer survival time for radiotherapy (54.0 Gy) followed by SMF chemotherapy as compared to SMF chemotherapy alone (42 versus 32 weeks, 1-year survival 41% vs. 19%) [27]. At the same time, Klaassen *et al*. saw no advantage in using combined 5-FU based chemoradiotherapy in comparison to chemotherapy with 5-FU alone (median survival: 8.3 vs. 8.2 months) [28]. Table 1 presents the randomized phase III studies on radiochemotherapy of locally advanced pancreatic cancer.

The postoperative and adjuvant treatment after curative resection of a pancreatic carcinoma will be discussed. Previous studies of the GITSG show a significant survival benefit when combined chemoradiotherapy is ued. However, these data have not been confirmed in any major European studies. An European Organization for the Research and Treatment of Cancer (EORTC) study by Klinkenbijl *et al*. showed an improved survival rate of 24.5 months in patients with postoperative chemoradiotherapy as compared to 19.0 months in the control group [29]. However, this difference was not significant. The data of the European Study Group for Pancreatic Cancer (ESPAC-1)

study publicized in 2001, showed a worsening of the survival rate under radiotherapy as compared to chemotherapy [30].
Among the chemotherapeutic agents used concurrently with radiation, 5-FU has long been regarded as standard medication, because its efficacy and tolerability have been well-documented and confirmed by numerous studies.

Concurrent Chemoradiotherapy with Gemcitabine

Even though several phase I and II studies have investigated gemcitabine-based radiochemotherapy, it has not yet been possible to establish a defined regimen either with respect to the dose and administration of gemcitabine or with regard to the treatment volume, fractionation and cumulative dose of radiation. The most common form of administration has been a weekly infusion of 30 minutes duration; at the same time, a twice-weekly application [31] or the application of a 24-hour continuous infusion [32] have also been investigated. Weekly doses of up to 600 mg/m^2 have been used when conventional single radiation doses were administered. In addition, the more toxic combinations with 5-FU, cisplatin, or mitomycin C have also been described (Table 2).
Concurrent radiotherapy has been most frequently administered in conventional fractionation with total doses of 40.0 to 50.4 Gy, whereas the use of hypofractionated (3x8 Gy) [33], accelerated (10x3 Gy) [34] or hyperfractionated regimens is also reported [35].
Therefore, it has to be emphasized that, in concurrent chemoradiotherapy, either the dose of gemcitabine or the radiation dose needs to be reduced. Otherwise, severe gastrointestinal complications such as ulceration or hemorrhage may be encountered, specifically when using fractions greater than 2.2-2.4 Gy [33, 34]. Increasing the weekly gemcitabine dose may also cause considerable gastrointestinal side effects. For weekly doses of up to 300 mg/m^2, only moderate gastrointestinal complaints such as vomiting and nausea have been reported, rising considerably when the gemcitabine dose was increased to weekly doses equal to 400 mg/m^2 or more [36, 37,38].
It is known from the previous administration of gemcitabine concurrent with the irradiation of the lung region that pulmonary toxicity depends greatly on the irradiated volume. As a result, Scalliet *et al*. reported 6 severe acute and 4 severe long-term complications in 8 treated patients with 3 therapy-related deaths [39]. In subsequent studies [40, 41] which strictly limit the target volume, lower toxicities were observed. Therefore, it can be concluded that the target volume is a critical parameter in the irradiation of the upper abdominal region when administered concurrently with gemcitabine. However, no studies are available for comparison in this regard. Most of the authors used a high target volume including loco-regional lymph pathways. In view of the very different dose and fractionation concepts, no comparable toxicities can be defined regarding the target volume.
Patients treated in our institution received concurrent chemoradiotherapy with 50.0 Gy applied to the macroscopic tumor and 45.0 Gy to the locoregional lymph nodes in 25 fractions. Concurrent chemotherapy was administered giving gemcitabine 300 mg/m^2 and cisplatin 30 mg/m^2 on days 1, 8, 22, and 29. The side effects of the treatment were limited mainly to the changes in blood tests. Whereas no serious gastrointestinal toxicities were observed, leukopenia Grade III and IV were seen in 60% and thrombopenia Grade III and IV in 51% of the patients. In 45 patients, a remission rate of 69% (9 complete and 22 partial remissions) was observed. In 30% of the primarily unresectable patients, it was possible to carry out a secondary R0 resection [6]. However, up to the present time it still needs to be assessed as to whether this locally effective treatment also improved overall survival.

Table 2. Chemoradiotherapy with gemcitabine for locally advanced pancreatic cancer.

Author	No. of patients	RT-dose	Gemcitabine dose (mg/m^2)	Median survival (months)	Response	Grade III/IV toxicities	Comment
McGinn (1998) [58]	13	50.4 Gy	200-400 1x/week	-	-	Leukopenia (n=1) Nausea (n=1) Gastroduodenal ulcer (n=1)	-
Wolff (1998) [38]	12	30 Gy (SD 3.0 Gy)	400-600 1x/week	-	PR=3/10	Nausea, vomiting, dehydratation (n=7)	Reduction to 350 mg/m^2
Blackstock (1999) [31]	18	45 Gy + 5.4 Gy Boost	20-60 2x/week	11	PR=3/18 NC=15/18	Neutropenia (n=4) Diarrhea (n=1) Nausea (n=3)	-
Hoffman (1999) [37]	18	50.4 Gy	300-600 1x/week	12	Resectable : 12/18	Thrombo-cytopenia (n=1)	Potential resectable Ca Postoperative preservation with gemcitabine 1,000 mg/m^2
Epelbaum (2000) [59]	20	50.4 Gy	400 1x/week	12	PR=4/20	Nausea (n=10) Diarrhea (n=10) Neutropenia (n=2)	Induction and preservation with gemcitabin 1,000 mg/m^2/wk
Reyes-Vidal (2000) [60]	14	45 Gy	200-325 1x/week	-	CR=2/14 PR=6/14	Diarrhea (n=2) Neutropenia (n=1) Anemia (n=1)	-
Wilkowski (2000) [61]	13	45 Gy	300 days 1, 15, 29 + 5-FU	-	PR=7/10	Neutropenia (n=8)	-
Talamonti (2000) [62]	7	45 Gy + 14.4 Gy Boost	50-100 1x/week + 5-FU	10	CR=0/7 PR=0/7	Nausea (n=4) Hemorrhage (n=2) Leukopenia (n=2) Thrombo-cytopenia (n=1)	-
McGinn (2001) [43]	37	24-42 Gy (SD 1.6-2.8 Gy)	1,000	11.6	CR=2/33 PR=8/33	Neutropenia (n=11) Thrombo-cytopenia (n=3) Gastro-duodenal ulcer (n=3)	-
Kornek (2001) [63]	15	45 Gy	100-160 1x/week (CI) + mitomycin C	8.3	PR=1/15 NC=10/15	Neutropenia (n=7) Thrombo-cytopenia (n=5) Diarrhea (n=2)	-
Yavuz (2001) [64]	10	45 Gy + 5.4 Gy Boost	60-120 2x/week + amifostin	9.2	CR=1/10 PR=5/10	Neutropenia (n=3) Thrombo-cytopenia (n=2) Gastro-intestinal (n=3)	-
Crane (2002) [34]	53	30-33 Gy (SD 3.0 Gy)	250-500 1x/week	11	-	Severe toxicity* (n=12) GI-bleeding: ulcer (n=3)	Secondary resection (n=6)

Table 2. Chemoradiotherapy with gemcitabine for locally advanced pancreatic cancer (continues).

Author	No. of patients	RT-dose	Gemcitabine dose (mg/m^2)	Median survival (months)	Response	Grade III/IV toxicities	Comment
Safran (2002) [65]	20	50.4 Gy	75-150 + paclitaxel	-	CR=1/10 PR=3/10 NC=5/10	Neutropenia (n=2/19) Thrombo-cytopenia (n=2/19) Nausea (n=3/19) Diarrhea (n=1/19) Pneumonitis (n=2/19)	-
De Lange (2002) [33]	24	24 Gy (3x8 Gy day 1,8,15)	300	10	CR=1/24 PR=6/24 NC=12/24	Gastro-duodenal ulcer (n=9) Fistula (n=1) Anemia (n=2) Neutropenia (n=2) Thrombo-cytopenia (n=4)	Preservation with gemcitabine 1,000 mg/m^2
Brunner (2003) [66]	36	50.4 Gy + 5.4 Gy Boost	300-600 days 2, 5, (12), (19), 26, 33 + cisplatin	14	PR=8/28 NC=20/28	Leukopenia (n=24) Thrombo-cytopenia (n=13) Gastro-intestinal (n=7)	Secondary resection (n=10/30)
Wilkowski (2003) [6]	57	45-50 Gy	300 days 1, 8, 22, 29 + cisplatin	14.8 (unresectable: 10.3)	CR=4/33 PR=19/33	Leukopenia (n=24/53) Thrombo-cytopenia (n=29/53)	Secondary resection (n=14/33)
Li (2003) [67]	18	50.4-61.2 Gy	600/week	14.5	CR=4/18 PR=5/18	Neutropenia (34%) Nausea (33%) Vomiting (17%)	Preservation with gemcitabine 1,000 mg/m^2

* Eight patients were admitted for supportive care longer than 5 days; 5 patients had more than 3 dose deletions of gemcitabine; 3 patients had gastrointestinal bleedings with evidence of gastric or duodenal ulceration. Four patients had two of the criteria for severe toxicity.
CI: continuous infusion
PR: partial remission
CR: complete remission
NC: no change
SD: single dose

Improving Systemic Efficacy of Concurrent Radio-Chemotherapy

Even with locally more intensive treatment (also including IORT), no improvement in overall survival rates has been achieved [42]. This is possibly explained by the early systemic dissemination of pancreatic cancer which ultimately determines the prognosis.
Following this rationale, McGinn *et al.* applied gemcitabine at its full cytotoxic dose (1,000 mg/m^2 weekly) in a clinical trial.
Assuming that the major effect of radiotherapy is achieved by control of the primary tumor and, in an effort to avoid increased toxicity, radiation was limited to the gross tumor only, leaving out the locoregional lymphatic drainage [43]. Keeping the duration of radiation constant at three weeks, individual fractionation was increased. This allowed the establishment of the application of 36 Gy in 2.4 Gy fractions as a tolerable regimen. The maximum dose level of 42 Gy given in 2.8 Gy fractions, which is roughly equivalent to a total dose of 50.4 Gy applied with a 1.8 Gy fractionation, proved to be too toxic. The response rate to this therapy was 18% (on completion of the therapy) and 33% following additional systemic chemotherapy. Average survival rates were 11.6 months and were therefore comparable with 5-FU based chemoradiotherapy. Despite the low volume

of irradiation, the rate of regional lymph node recurrence was low (3/37 patients). Local tumor progression occurred in 7 of 37 patients. The progression of the disease was influenced mainly by the metastases (in 25 of 37 patients). The authors therefore concluded that low volume radiotherapy has not resulted in excess locoregional failure with intensive systemic therapy, especially when considering the potential toxicity of the treatment.

Blackstock *et al*. conducted a phase I study where gemcitabine was given twice weekly together with concurrent radiotherapy (45.0 Gy large volume, 5.4 Gy boost). The maximum tolerated dose was 40 mg/m^2 of gemcitabine. The median survival rate of 11 months is, however, comparable to other chemoradiotherapy regimens.

Even if it is very problematic to draw conclusions as to the survival without available phase III studies, it may nevertheless be concluded that, regarding the survival times, a single superior regimen of gemcitabine-based chemoradiotherapy has not been defined so far.

Local Spread of the Tumor

Pancreatic cancer infiltrates the adjacent peripancreatic or retroperitoneal tissue already at an early stage. In addition, there is frequently perineural infiltration as well as an invasion of local lymphatic vessels.

The local lymphatic drain from the pancreas consists of a peripancreatic first node and a perivascular second node along the *A. mesenterica sup, A. gastroduodenalis, A. hepatica communis*, as well as the *A. lienalis* and *truncus coeliacus*. Because of their close proximity, the paraaortal and paracaval lymph nodes as well as the lymph nodes of the vena *portae hepatis* are also frequently affected [44]. According to the International Union Against Cancer (UICC) classification, the peripancreatic lymph nodes are divided according to their location into superior and inferior (above or below the head or body of the pancreas, respectively), anterior (anterior pancreaticoduodenal, pyloric and proximal mesenteric lymph nodes) and posterior (posterior pancreaticoduodenal lymph nodes) as well as into lymph nodes along the *ductus choledochus* and proximal mesenteric lymph nodes, lienal nodes (for tumors of the pancreas *corpus* and *cauda*), and also celiac lymph nodes (for tumors of the pancreas head).

The risk of invasion of the locoregional lymph nodes ranges between 76% and 83% according to analyses of histological specimens carried out in Japan [45, 46]. In 15-20% of cases, an affection of the paraaortal lymph nodes is also to be expected [44, 45]. However, in pre-operative diagnoses, the suspicion of lymph node involvement was only observed in about one-third of all cases.

The high risk of lymph node metastasis indicates that there might be the necessity of extending the clinical target volume beyond the macroscopic tumor to the regional lymph nodes, even though there are no comparative studies available on the risk of a lymph node relapse following small volume radiation.

It should be mentioned in this regard that, in patients treated with IORT after resection (partly complemented with external chemoradiotherapy), local recurrences occurred in 30-50% [18, 19, 47]. These can most likely be evaluated as local lymph node recurrences on the basis of the high dose administered with IORT in the tumor bed.

Definition of Target Volume and Radiation Treatment Planning

A 3-dimensional conformal radiation treatment plan is required to guarantee the optimal protection of the adjacent radiosensitive organs. Positioning and immobilization aids are used to ensure stable and reproducible positioning despite raised arms in order to facilitate lateral radiation angles and the resulting lordosis of the lumbar spine.

In correspondence with the rapid lymphatic spread of the pancreatic tumor, loco-regional radiation (CTV-II) should include the superior, inferior, anterior and posterior pancreaticoduodenal, pyloric, celiac, and

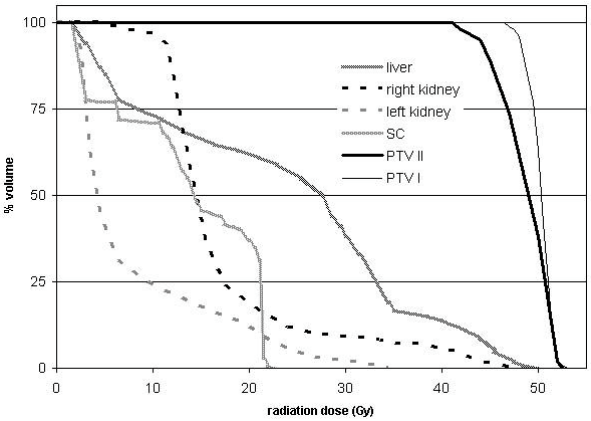

Figure 1. Dose-volume-histograms of the tumor-region (PTV I) with regional lymphatic pathways (PTV II) and relevant organs at risk (SC = spinal cord).

proximal mesenteric lymph nodes as well as those of the *ductus choledochus* and the paraaortic lymph nodes in the region. In the case of a carcinoma of the pancreatic *cauda,* or respectively body and *cauda*, the superior, inferior, posterior pancreaticoduodenal, proximal mesenteric, and lienal lymph nodes are to be included. It is rare for the retrocrural and retrocaval lymph nodes to be affected. For that reason, there is no need for them to be included as standard in the target volume.

Investigations of organ motility and respiratory movement showed a considerable positioning variability of the organs in the upper abdomen. The positioning variability at the pancreas which is dependent on respiration occurs mainly in the cranio-caudal direction (up to 2.4 cm) [48]. It is less distinctive in the lateral and anterior-posterior direction. Positioning variabilities independent of respiratory motion have been seen especially on the pancreatic body and tail, as well as on the *A. mesenterica sup*. These are associated with the peristalsis, and the filling of the stomach and the intestines, respectively. [49]. Because of respiratory movement, intestinal motility, and variability in the positioning, a safety margin of 2-3 cm should be added to the clinical target volume (CTV II).

The craniocaudal range of the irradiation fields typically extends from the level of the *porta hepatis* to the level of the junction of the *V. mesenterica inferior*. The lateral and ventrodorsal extent of the field has to be determined on the basis of pretherapeutic CT or MR imaging. Limited irradiation of the tumor or a boost treatment should encompass the macroscopic pancreatic tumor plus a safety margin of about 1 cm. With the help of dose volume histograms, the dose in adjacent organs at risk (liver, kidneys, spinal cord) should be assessed in order to prevent exceeding tolerance levels (Figure 1). According to Emami *et al*. [50], the tolerance dose of TD5/5 for the liver is 50 Gy, 35 Gy, 30 Gy for 1/3, 2/3 or 3/3 of the organ volume, respectively. Newer investigations, using mathematical models to estimate the normal tissue complication rate (NTCP), indicate a higher tolerance of the liver tissue, at least in the irradiation of partial volumes [51]. Dawson *et al*. [52] indicated a 5% risk of radiogenic liver damage at 90 Gy, 47 Gy or 31 Gy for 1/3, 2/3 or 3/3 of the liver volume, respectively. On the other hand, pancreatic cancer patients frequently have prior damage to the liver parenchyma as a consequence of cholestasis and perfusion deficits. The tolerance of the liver may also be further reduced due to concurrent chemotherapy. For that reason, we reduce liver exposure to a maximum of 12.5 Gy in 75%, 25 Gy in 50%, and 37.5 Gy in 25% of the liver volume, respectively, in our institution. Temporary radiogenic hepatosis occurred only occasionally (less than 5%) in our patients, thus keeping within these limits. We have not seen long-lasting liver function damages.

For the kidneys, Emami *et al*. stated tolerance doses of TD5/5 of 50 Gy, 30 Gy, or 23 Gy for 1/3, 2/3, or 3/3 of the organ volume, respectively. Even if the risk of clinical nephropathy seems to be limited by a partial exposure to 25-40 Gy, it is nonetheless possible that a major reduction of the creatinine clearance may be induced [53]. Concurrent chemotherapy, specifically the use of cisplatin and other nephrotoxic agents (e.g. aminoglycoside antibiotics) can significantly reduce the tolerance level of the kidneys [54]. For this reason, we take care not to expose 30% of a kidney to more than 20 Gy. No radiogenic nephropathies were observed in

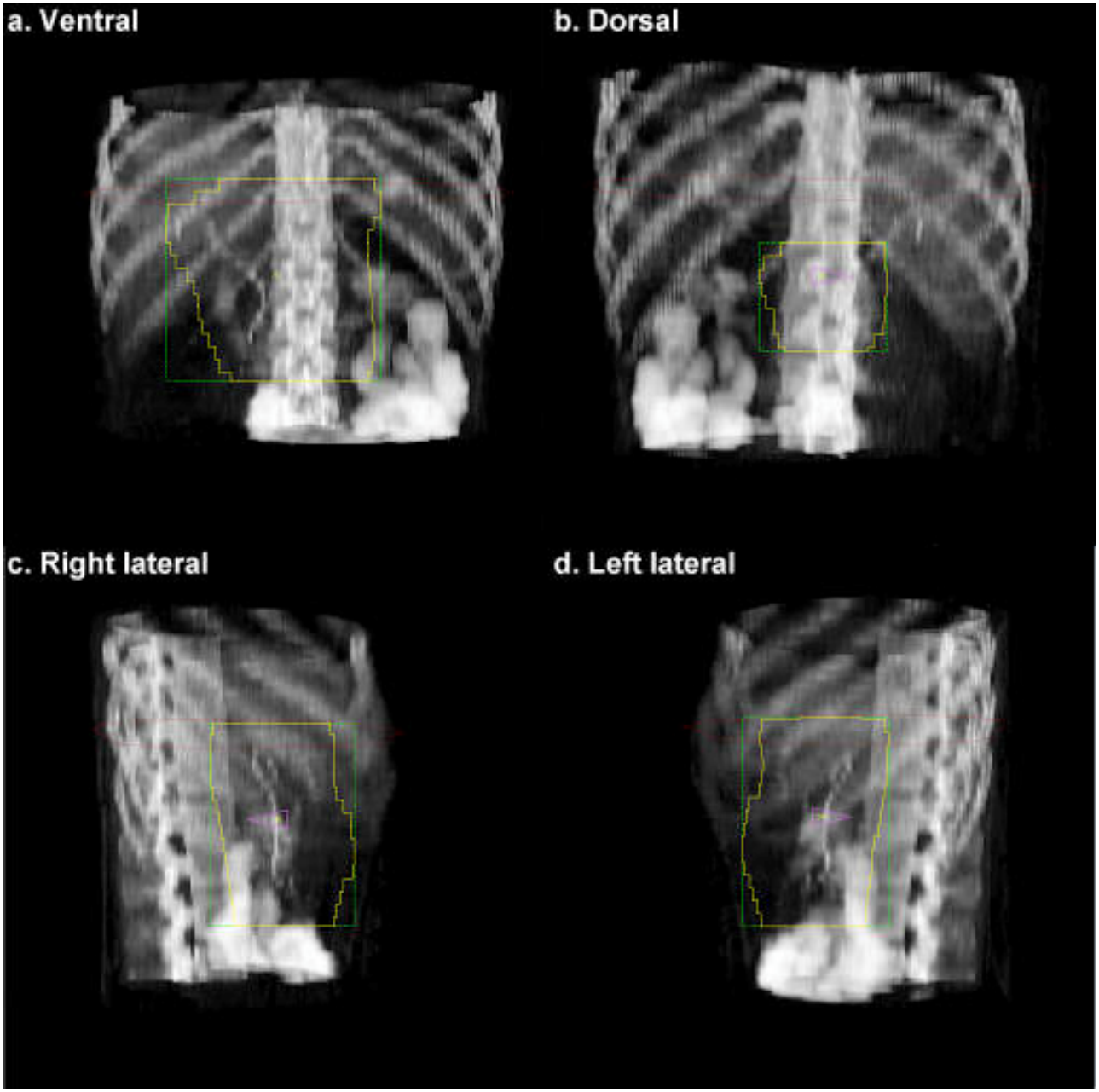

Figure 2. DRR-images showing a four-field-treatment-plan for a patient with cancer of the pancreatic head (see Figure 3). Via the dorsal supplementary-field a higher dose is applied in the tumor-region. In this area 2.0 Gy are given per fraction whereas the loco-regional lymph-nodes received 1.8 Gy. A total of 50.0, respectively. 45.0 Gy were administered. Green lines: open field which will be modeled individually with the multi-leaf-collimator (yellow border). (Turquoise triangle: use of a wedge filter for dose optimization.)

our patients in this regard. In addition, prior to starting the therapy, kidney clearance should be checked, if possible for each kidney separately with an isotope nephrogram in order to take individual differences in kidney function into account in planning radiation treatment.

It is generally no problem to keep the tolerance dose of the spinal cord to about 40-50 Gy through the use of multi-field techniques. In order to keep acute and late gastrointestinal reactions to the minimum possible, maximum protection of the small intestine should be aimed at in planning radiation treatment. Specifically, in the case of pre-existing adhesions (e.g. from previous operations), reduced intestinal motility can result in a higher exposure of individual intestinal sections with an associated higher risk of complications. As a basic principle, a

planning CT (slice thickness between 0.5 and 0.8 mm) with sufficient intestinal contrast should form the basis for planning radiation treatment. The use of i.v.-contrast can be helpful in exactly demarcating the tumor and visualizing vessels and lymph node regions.

Dependent on the range of the target volume and the relation to the anatomical position of the kidneys and the liver, the main technique used is a non-orthogonal 3-4 field technique with one ventral, two lateral, and possibly also an additional dorsal irradiation field (Figure 2). Under unfavorable anatomical conditions, significantly more fields may be required from different irradiation angles (e.g. using the half-field asymmetric technique). The dose should be specified in accordance with ICRU-50 (International Commission on Radiation Units and Measurements) and its requirements regarding the homogeneity of dose distribution should also be fulfilled.

With the same total number of fractions, a "field-in-field" irradiation technique can achieve an increase in the individual dose in CTV I, while maintaining the target dose in CTV II. The central volume comprises CTV I, and the peripheral volume CTV II. Because of the small partial dose proportion of the central field, the dose within this volume can be modified. The dose in the ICRU reference point is defined commensurate with the target dose in CTV I.

In the Munich study (a phase II study to compare chemoradiotherapy using gemcitabine/cisplatin with chemoradiotherapy using 5-FU in patients with locally advanced unresectable pancreatic carcinoma) (doses of 50.0 Gy in CTV I and 45.0 Gy in CTV II are aimed for. In 25 individual fractions over 5 weeks, a dose of 2.0 Gy is defined as the ICRU reference point; with field weighting, an isodose of at least 95% covers the area of CTV I, whereas, as a minimum requirement, CTV II is included in the 85% isodose. An irradiation which conforms to ICRU-50 is thus administered in CTV I. The dose of CTV II can only be defined in line with the surrounding isodose. In line with IMRT radiation treatment planning, compliance with

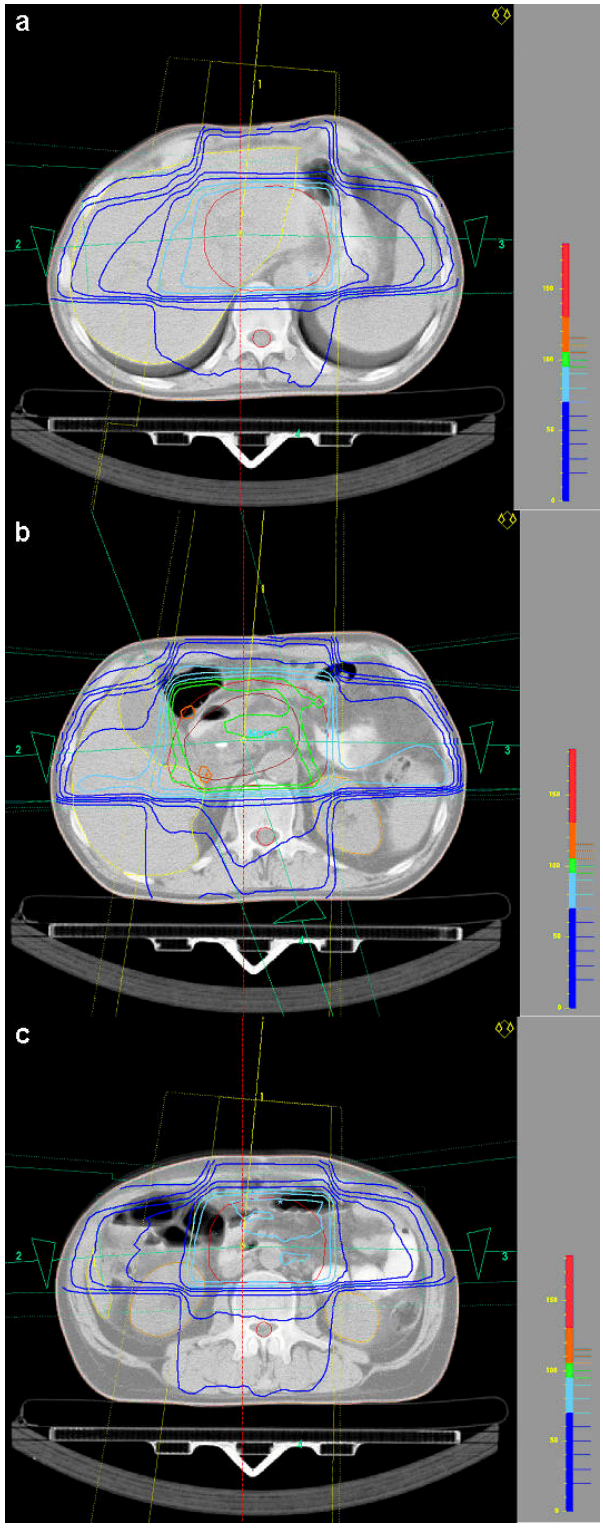

Figure 3. 3D-conformal treatment planning in a patient with unresectable cancer of the pancreatic head. Horizontal slize in upper field boundary (**a.**), central ray level (**b.**) and in lower field boundary (**c.**). Gross tumor volume (enclosed by the 100%-isodose) and tumor with locoregional lymph nodes (enclosed by the 90%-isodose) were marked as treatment volumes. Radiotherapy is administered with 4-field arrangement.

ICRU-50 criteria regarding dose homogeneity is aimed for. Strictly speaking, this dose specification (of CTV II) does not comply with ICRU-50 criteria, but it has proven its practical value in the clinical routine of radiation treatment planning. For clarification, Figure 3 shows a radiation treatment plan which has been drawn up on the basis of this dose regimen.

Future Prospects: Intensity-Modulated Radiotherapy (IMRT)

IMRT and inverse radiation treatment planning may open new opportunities to apply higher and more homogenous doses within the tumor region while, at the same time achieving a lower exposure in adjacent critical structures, especially in the small intestine [55]. A first phase I study using concurrent gemcitabine (350 mg/m^2) as a radiosensitizer and escalating doses of IMRT yielded disappointing results [56]. Dose-limiting toxicities occurred already at the first level (33 Gy in 11 fractions) and were also observed after the gemcitabine dose had been reduced to 250 mg/m^2.

At the present time, it is not yet possible to predict whether the expectations which IMRT had raised will be fulfilled in the radiation therapy of pancreatic cancer. The need to define the CTV liberally because of the variability in positioning and the difficulty in defining the macroscopic tumor region speaks against the advantages of IMRT, namely, that high irradiation doses will be administered in a closely defined region.

Conclusions

It can be concluded that, with modern techniques in the planning and application of radiation treatment as well as keeping the dose tolerances both in radio- and chemo-therapy, chemoradiotherapy of pancreatic carcinomas can be administered safely and with an acceptable level of tolerance.

Even if there is no comparative data available, the high risk of involvement of the loco-regional lymph nodes speaks in favor of their inclusion in the clinical target volume. It is common to use conventional fractionation regimens with a total dose of 45.0-50.4 Gy in CTV II, possibly supplemented with a small volume boost in the tumor region of e.g. 5.4 Gy. With the help of IMRT, further organ protection (especially of the small intestine) might be achieved, even though there is no evidence of this at present.

With respect to concurrent chemotherapy, 5-FU may still be regarded as the standard medication, with a dose of 200-350 mg/m^2 per irradiation day. Meanwhile, promising data are available regarding gemcitabine-based chemoradiotherapy. However, the optimal dose and application of this radiosensitizing agent as well as an additional combination partner still need to be defined.

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Abbreviations 5-FU: 5-fluorouracil; CRT: chemoradiotherapy; CTV: clinical target volume; EBRT: External Beam Radiation Therapy; EORTC: European Organization for the Research and Treatment of Cancer; ESPAC: European Study Group for Pancreatic Cancer; FAM: 5-fluorouracil, adriamycin/doxorubicin, mitomycin C; GITSG: Gastrointestinal Tumor Study Group; HR: hazard ratio; ICRU: International Commission on Radiation Units and Measurements; IMRT: intensity-modulated radiotherapy; IORT: intraoperative radiation therapy; NTCP: normal tissue complication rate; SMF: streptozotocin, mitomycin C, 5-fluorouracil; UICC: International Union Against Cancer

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