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REVIEW ARTICLE

# Individualized radiotherapy (*i*RT) concepts for locally advanced pancreatic cancer (LAPC): indications and prognostic factors

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**Abstract**
*Background* Novel techniques in radiation oncology have significantly improved the therapeutic window in locally advanced pancreatic cancer LAPC. In about one third of the patients, chemoradiation can lead to secondary resectability, contributing to an increase in outcome. Dose-escalation approaches using stereotactic body radiotherapy (SBRT) or advanced treatments such as intensity-modulated radiotherapy (IMRT) can exploit the biological benefits of hypofractionation, or use "dose painting" approaches to target defined subvolumes. Prognostic subgroups of patients have been identified, based on molecular markers such as CA 19–9, nutritional factors, diabetes or immunological properties of tumor and normal tissue.
*Purpose* The aim of the present manuscript is to summarize data on downsizing for locally advanced pancreatic cancer (LAPC) and to elucidate the role of individualized radiotherapy (*i*RT).
*Conclusion* Future concepts focus on *i*RT based on prognostic factors leading to a true personalized treatment.

**Keywords** Neoadjuvant chemoradiation · Locally advanced pancreatic cancer · Stereotactic body radiotherapy (SBRT) · Radiotherapy · Personalized medicine

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## Introduction

Locally advanced pancreatic cancer (LAPC) remains a challenging clinical situation: On the one hand, the patient presents with non-metastasized disease which points in the direction of long-term survivorship, but also demands for effective local treatment. On the other hand, the most effective therapeutic intervention leading to "cure" is not reasonably possible, which is complete surgical resection. Only about 15–20 % of all patients diagnosed with pancreatic cancer can be categorized as resectable [1, 2]. It is known that oncological complete resection is the strongest prognostic factor; however, due to the locally advanced growth pattern, blood vessels and nerves are encompassed by the tumor limiting resectability in the majority of cases. Thus, strategies to increase the rate of complete resection are an important leverage to significantly improve outcome.

There are several strategies: Firstly, a local tumor (without distant spread) requires local treatment intensification. For that, radiation therapy (RT) is the ideal means in terms of dose escalation. This requires modern highly precise techniques, which have been developed over the last years. Novel imaging identifying gross tumor volumes (GTV) as well as normal tissue, and characterizing tissue subregions which are more aggressive than others, such as hypoxic regions are helpful. Improvements in MR-Imaging as well as PET methods will have to be evaluated for this means. Secondly, it is necessary to identify prognostic factors determining outcome in these patients. Molecular markers or other tissue parameters of the tumor itself or the surrounding microenvironment, immunological properties of tumor and normal tissue, tumor markers, or other patient-specific characteristics will help stratify patients in the future for dose-escalation strategies, de-escalation protocols, combination approaches with systemic treatments, as well as immunologic regimens leading to a truly

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personalized oncological treatment including an individualized RT (*i*RT) concept.

## Technical development in radiation oncology: image guidance and dose escalation

In the past, RT was 3D-based on CT imaging. 3D-conformal RT lead to visualization of dose to target volumes and normal tissue, which was a significant improvement compared to prior 2D-RT. However, the conformity of 3D-RT may be limited especially in cases of complex anatomy, thus, although older studies but at that time advanced studies used these techniques, doses to normal tissue limited dose escalation to the tumor: For 3D-treatment planning of photon radiotherapy, target volume definition as well as definition of organs at risk (OAR) is performed on each slice of the 3D-data cube; beam angles for radiotherapy are chosen to reach a high conformity around the target volume and to spare normal tissue. Usually, 3–5 beams are used for treatment. Generally, for LAPC, the GTV is treated encompassed by a clinical target volume (CTV) including typical regions of tumor cell spread as well as lymphatics.

The advent of stereotactic radiotherapy (SRT) significantly improved precision; it was initially developed by the neurosurgeon Lars Leksell in Sweden for radiosurgery of brain tumors [3–8]. The benefit of SRT is the highly precise delivery of RT with a steep dose gradient toward normal tissue; thus, high local doses can be applied within a single fraction concept, or as fractionated regimens to exploit the benefit of fractionation in terms of side effect reduction, especially in the brain and skull base region. SRT was then transferred into the extracranial regions (stereotactic body radiotherapy, SBRT), and is today well established for lung and liver tumors [9–11]. There, also hypofractionated regimens have been evaluated; this means higher single doses are applied and the total number of treatment days can be reduced: Such short courses of RT, commonly using 3–8 fractions have certain biological benefits: Fractionated courses of RT to a tumor and surrounding tissue at risk use the repair capacity of normal tissue between fractions to reduce the risk of side effects. For small lesions, higher single doses can be applied, and although there is much controversy about the dose–response relationship, it has been shown that the proportion of cells killed appears to increase at least exponentially with dose, accompanied by a destruction of vascular endothelium. Thus, high single doses can be more effective than fractionated treatment. However, the limitation is they should only be applied to smaller treatment volumes to avoid side effects to normal tissue.

Several groups have evaluated SBRT protocols for pancreatic cancer; it became increasingly possible since elective irradiation of lymph nodes has moved out of focus, and treatment volumes thus got smaller. The main advantage in the case of pancreatic cancer, however, is the shortened treatment time, not postponing full-dose chemotherapy. The majority of series are retrospective analyses; however, at least seven prospective trials of SBRT in pancreatic cancer exist [12]. Fractionation ranges from radiosurgery with single doses between 15 Gy and 25 Gy; and hypofractionated regimens range from three to six fractions. The largest series is by Chang et al. on 77 patients treated with single doses of 25 Gy with 6 and 12 months survival from SBRT of 56 and 21 % [13]. A follow-up study combined single fraction SBRT with chemotherapy, with a median survival of 11.8 months and only one patient with Grade 2 or higher gastrointestinal toxicity (duodenal ulcer; [14]). The largest group of fractionated SBRT included five fractions, with median survival 16.4 months versus 15 months with and without surgical resection [15]. In general, early toxicity was limited in most studies; however, substantial rates of long-term gastrointestinal side effects were observed [12]. Therefore, at the moment, although data is promising, SBRT can be considered an experimental treatment as is recommended within clinical trials only.

With intensity-modulated radiotherapy (IMRT), additionally, intensity modulation is added within each radiation field; thus, even with complex-shaped anatomy, dose conformity can be increased [16]. This can be used not only to modulate the dose away from healthy organs, i.e., intestines, kidneys, but also to escalate the dose in terms of an integrated boost to defined regions, i.e., macroscopic tumor, PET-positive regions, hypoxic regions, etc. Due to the improved dose distributions, side effects may be reduced: Retrospective data comparing 3D- and IMRT-treatments with comparable dosing regimens, however, did not show a significant reduction of side effects [16]. An extensive review by Brunner and colleagues could reveal that the majority of side effects (i.e., nausea/vomiting, diarrhea, and late GI toxicity) are tentatively lower with IMRT, but without improvement of clinical outcome [17].

However, IMRT can be used for "dose painting" increasing the dose to defined subregions, such as hypoxic areas, or areas of the GTV when possible. These concepts are currently being explored within prospective trials.

## Clinical data of neoadjuvant chemoradiation

In the past, chemotherapy alone was administered, using substances such as gemcitabine (GEM) or 5-FU. Still to date, no randomized controlled trial has confirmed the real benefit of neoadjuvant chemoradiation in LAPC. Mostly, GEM is applied in combination with RT at weekly doses of 300 mg/$^2$ due to the fear of severe side effects when combining full-dose GEM with RT [18–30].

Several groups have applied chemoradiation with acceptable toxicity and convincing outcome. Older data obtained by

the GITSG study established the role for RT and chemotherapy with bolus 5-FU, comparing split-course RT (40 Gy total dose) with chemotherapy to radiation (60 Gy total dose) together with chemotherapy or RT alone: Median survival was prolonged from 22.9 to 42.2 weeks [7]. Following trials focused on the optimization of 5-FU application, and most newer study concepts have moved away from of split-course RT. GEM was integrated as a radiation sensitizer in pancreatic cancer [8–12], and several studies have shown that GEM and RT lead to comparable results than 5-FU and RT [13, 14].

Several other combination study designs have been performed: For example, a trial evaluating the clinical outcome after RT, GEM, and cisplatinum in patients with locally advanced pancreatic adenocarcinoma could show acceptable toxicity; however, no benefit compared to other single-agent chemotherapeutic schedules could be determined [15]. With respect to preoperative chemoradiation, a retrospective analysis performed by the MD Anderson Cancer Center revealed that in even in resectable patients, preoperative RT is not disadvantageous, and since postoperative recovery often extends the time until (about 25 % of all patients) adjuvant treatment can be initiated [16]. Additional arguments for neoadjuvant radiochemotherapy before any surgical resection are the increase in complete oncological resections due to tumor shrinkage, selection of patients with more stable disease for surgery, treatment of micrometastases, and treatment of tissue not modified by surgery and potentially more sensitive to chemotherapy and RT [16–18]. The MD Anderson group published a median survival of 21 months, with 31 % of all patients with no evidence of disease, in 132 patients treated with preoperative chemoradiation followed by surgical resection [19]. Several meta-analyses and reviews have been conducted regarding this topic. Gillen et al. extensively reviewed the literature and included 111 studies for evaluation, of which 104 included RT in the neoadjuvant concept. The data show clearly that approximately one third of patients show clinical and radiographic response, compared to 5–15 % after chemotherapy only [1]: For LAPC, around 33.2 % of all patients convert to resectable patients after neoadjuvant chemoradiation. An analysis of 215 patients showed that secondary resection was possible in a high percentage of all patients, and overall survival was increased significantly in these operated patients from a median of 11.9 months to a maximum of 22.1 months following complete removal of the tumor. This fact underlines the high importance of oncologically complete margin-free interventions which is the strongest prognostic factor [19]. The study by Sho et al. focussed on 184 consecutive patients treated with surgery for pancreatic cancer, of which 85 had received neoadjuvant chemoradiation with a GEM-based regimen. Compared to most other studies, however with full-dose GEM 1,000 mg/m$^2$ per week [31]. Neoadjuvant chemoradition lead to favorable pathological responses compared to the surgery-only group; however, the benefit in terms of survival was significant in primarily resectable tumors, but not in borderline-resectable tumors. The improved outcome after neoadjuvant chemoradiation may also be due to the response in lymphatics: Roland et al. reported that reduced lymph node ratios are seen after neoadjuvant chemoradiation compared to up-front surgery; although this was shown in a group of resectable patients, this potentially also holds true for primarily irresectable patients undergoing secondary resection [32].

Novel substances such as nanoparticle albumin-bound (nab)-paclitaxel (Abraxane, Celgene, Summit, NJ) have been developed: nab-paclitaxel is a microtubule inhibitor, as is paxlitaxel. It has shown promising efficacy first in patients with metastasized pancreatic cancer [26, 33–39]. Thus integration into a neoadjuvant concept (with or without additional chemoradiation) will be a promising treatment approach and is currently being investigated.

To date, within treatment recommendations for locally advanced pancreatic cancer without distant metastases, chemoradiation or RT alone can be found; in the US-treatment guidelines chemoradiation is tightly anchored whereas in the European guidelines the recommendation for neoadjuvant chemoradiation is not as clear and recommended within clinical protocols.

Until now, data from directly randomized trials are still lacking. Currently, the CONKO-007 trial is recruiting: This randomized trial examines the effectiveness of chemoradiotherapy compared to chemotherapy alone after induction chemotherapy with three cycles of GEM or six cycles of FOLFIRINOX (Folinic acis, 5-FU, Irinotecan, Oxalopatin) in patients with locally advanced, non-resectable, and non-metastatic pancreatic cancer. This trial takes into account the data from GEM-base chemoradiation, as well as the emerging data from FOLFIRINOX in different clinical stages of pancreatic cancer [26, 40–46].

## Prognostic factors determining outcome

The search for real prognostic factors in pancreatic cancer is actively ongoing in several fields including lifestyle factors, pathological features of the tumor and of the surrounding micormilieu, as well as molecular determinants and immunologic characteristics.

In general, it is known that body weight and weight loss associated with disease are associated with a reduced overall outcome. This has been shown also in patients with pancreatic cancer; however, to date, no large-scale randomized prospective data with active nutritional intervention exist [18, 47]. However, in spite of the strenuous treatment, it has been shown that nutritional status and appetite/weigth loss can improve over the 6–7 week treatment course [18, 48]. If this is not the case, patients are associated with a reduced outcome.

In general, weight loss as a main factor of cachexia is linked to poorer response to any treatment as well as decreased survival [49]. Body composition is linked to a variety of factors despite the tumor disease itself, such as diabetes/insulin resistance or anemia [50, 51]. A study by Di Sebastiano evaluated 50 patients with pancreatic cancer with focus on weight loss, diabetes, anemia including evaluation of CT-scans. The study revealed a strong correlation between diabetes and anemia, with both factors being linked to accelerated loss of muscle tissue and visceral adipose tissue (VAT;[51]). Clinical biomarkers are necessary to personalize nutritional supplementation and aggravate diabetic medication to prevent accelerated muscle and adipose tissue regression.

Besides life style and nutritional hallmarks, tumor markers are in focus for *i*RT concepts: The well established tumor marker CA-19-9 has been shown in several studies to strongly correlate with outcome, and is the most widely used tumors marker: Higher levels are associated with a reduced response to chemoradiation in terms of secondary resectability compared to lower pre-treatment levels [18]. In several studies the impact of CA 19–9 was demonstrated: A level of 180 U/ml of CA 19–9 was identified as a cutoff level predicting outcome. Patients with levels below are associated with a higher outcome than patients with higher levels [52]. The prognostic value is underlined by the fact that several clinical trials include CA 19–9 levels and response kinetics of CA 19–9 as secondary endpoints within the trials, e.g., RTOG 9704 [53–55]. Also for the currently recruiting CONKO-007 trial on neoadjuvant chemoradiation CA 19–9 levels are part of the inclusion criteria.

Only recently, Carbohydrate antigen 72–4 (CA 72–4) could be identified as a prognostic factor in patients with LAPC treated with chemoradiotherapy; CA 72–4 is a human tumor-associated glycoprotein which is a a tumor marker for diagnosing and predicting outcome in gastric and ovarian cancers [56]. The group from Johns Hopkins evaluated pancreatic tumor tissue specimens and could show that tumoral loss in ATM (ataxia teleangiectasia-mutated gene) together with normal levels of TP53 are associated with significantly reduced survival [57]; moreover, tumoral loss of ATM is more frequent in familial pancreatic cancer than in sporadic. However, no data to date is available to identify a distinct radiosensitivity of radioresistance of such cell subtypes.

Besides tumor markers, other candidate molecules as biomarkers include SMAD-4, stromal secreted protein acidic and rich in cysteine (SPARC) or hENT-1 (human equilibrative nucleoside transporter 1), all of which have shown some impact on outcome in different clinical situations of pancreatic cancer [58–68]. Often however, data is controversial between centers, as has been shown for interferon alpha/beta receptors [69–72].

Newer data elucidates the connection between stem cells and outcome in pancreatic cancer: Mizukami and colleagues evaluated the tumor tissue of patients treated with neoadjuvant chemoradiation and showed that CD 133 and ALDH1 expressions are prognostic factors for survival, with higher expression correlating with reduced outcome [73]. Again, in contrast, other groups have reported controversial data on the relevance of ALDH1 in pancreatic cancer [74, 75]. Subgroup analysis have shown that CD44 and ALDH-1 positive cells may be hallmarked by a specific resistance to chemoradiation [73].

## Novel RT concepts

Novel RT concept include methods of safe dose escalation in combination with improved imaging as well as personalized appraoches based on molecular or other patient-specific parameters.

Novel beam qualities, such as particle therapy, may offer treatments optimization. There, is must be differentiated between proton and higher-LET RT such as carbon ion beams. For protons, the biological efficacy can be considered comparable to photons, with a relative biological efficacy (RBE) of about 1.1 [76]. Particles are characterized by a so called inverted dose profile, with a low energy deposition within the entry channel of the beam, and a high local dose depostion within the Bragg Peak. These facts lead to an altered dose distribution pattern, reducing areas of low and intermediate dose to normal tissue. This reduction of integral dose is hypothesized to reduce long-term side effects, which is predominanlty important in young patients (such as children) and long-term survivors.

To date clinical evidence is not yet available to support such hypotheses. On the other hand, particle beams are sensitive to any motion, such as gastrointestinal organ movement, changes in air- and liquid filled cavities, as well as volume changes during treatment [77–80]. Such interactions can lead to so called interplay effects, distorting the “planned” dose distribution. Currently, several research groups are working on improving motion management for clinical application.

Compared to protons, carbon ions offer a higher RBE, which for pancreatic cancer is between 2 and 5 [81]. Is has been shown that carbon ion RT may lead to an increased outcome in selected radioresistant diseases such chordomas and chondrosarcomas, adenoid cystic carcinomas, or melanomas [31].

In Japan, several clinical trials have been performed to evaluate proton or carbon ion radiotherapy for pancreatic cancer alone or in combination with chemotherapy.

Several proton centers have evaluated proton radiotherapy for pancreatic cancer: Dose planning comparisons have elucidated to possibility to reduce dose to normal tissue, such as the intestine, which potentially reduces acute side effects and offers the potential to increase the dose of concomitant chemotherapy [82–84]. First data have shown very low rates of gastrointestinal toxicity; however, no large series and comparative

clinical data are currently available [85–87]. The Hyogo Particle Center performed a study on feasibility and efficacy of GEM-based chemoradiation with protons in LAPC. Three dosing schemes were used and GEM was applied at a dose of 800 mg/m$^2$/week for 3 weeks. After a median follow-up time of 12.5 months, six patients (12 %) observed acute hematologic or GI toxicities, and grade 3 or greater late gastric ulcer and hemorrhage were seen in 5 patients (10 %). Local progression-free survival, progression-free survival, and overall survival rates were 81.7, 64.3, and 76.8 %, respectively [88]. To shorten treatment times, hypofractionated proton radiotherapy is being evaluated within clinical trials: A dosing scheme of 5×5 Gy E has shown only 4.1 % of Grade 3 side effects with favorable local control; KRAS-status and high CXCR7-expression, circulating CEA, CA 19–9 as well as HGF-levels correlated with poor outcome [89]. Randomized trials comparing with advanced photons (IMRT, SBRT, or other) are still lacking.

In Chiba, 22 patients with localized, resectable adenocarcinoma of the pancreas were treated with preoperative carbon ion radiotherapy with total doses of 44.8 Gy E to 48 Gy E (2.8 Gy E or 3.0 Gy E per fraction). Local control rate was 100 %, overall survival was 59 % at 1 year. Patients receiving surgery demonstrated 86 % overall survival compared to 3 % without surgery [32]. The following trials applied 30 Gy E to 35.2 Gy E in 8 fractions, overall survival at 1 and 5 years in patients treated with surgical resection after preoperative carbon ion radiotherapy was 89 and 51 %, without any local recurrences [32]. The following trials stepwise increase local dose 38.4 Gy E to 52.8 Gy E in 12 fractions and weekly GEM was increased from 400 mg/m$^2$ to 1000 m$^2$. Acute hematological toxicity as well as non-hematological side effects were low without any grade 4 and 5 toxicities. Only in the 700 mg/m$^2$ and 1,000 mg/m$^2$ GEM arm, 3/6 (50 %) and 8/12 (75 %) developed grade III hematological toxicity. Local control was comparable for are dosing levels of RT, survival was higher with increasing GEM doses [32].

However, inspite of these data, carbon ion radiotherapy must be considered an experimental treatment for pancreatic cancer and should be performed within clinical trials only.

## Conclusion and essential prerequisites for *i*RT concepts in LAPC

Future research will focus on highly precise, biologically personalized *i*RT concepts (Fig. 1). This requires solid and reliable biomarkers.

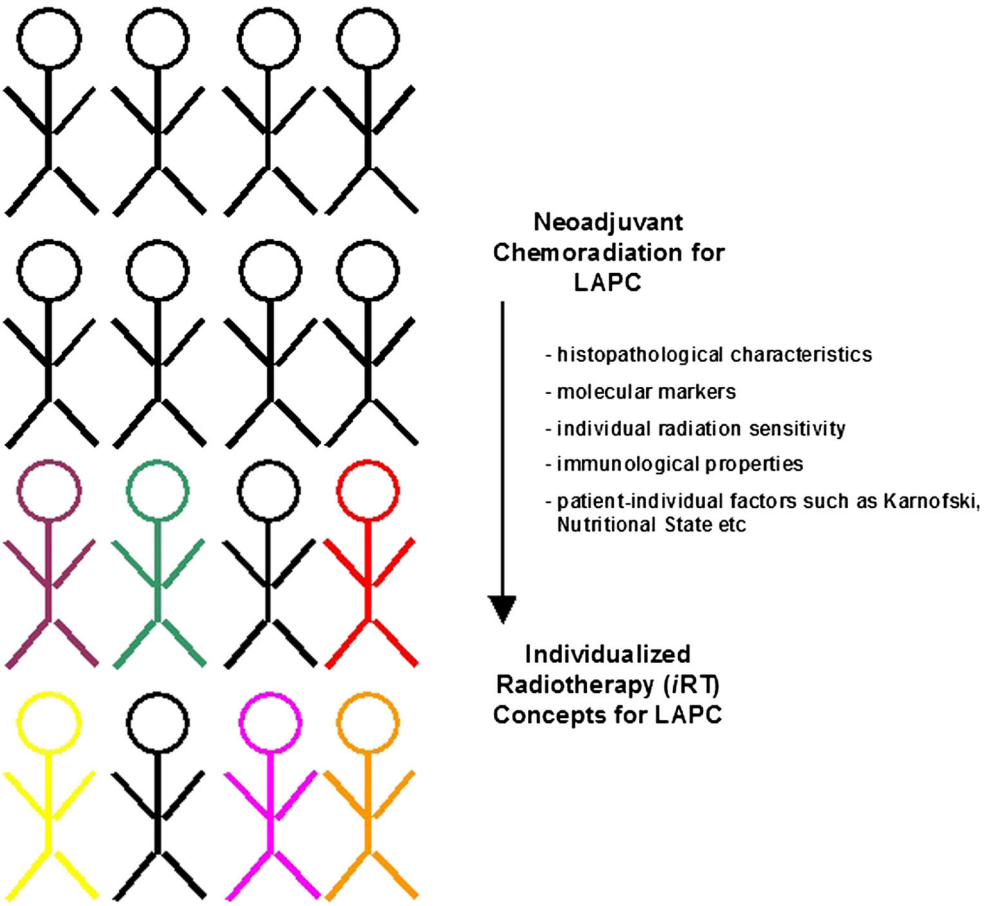


**Fig. 1** Prospective trials for individualized radiotherapy concepts for LAPC

Since patients generally do not undergo surgical intervention prior to treatment, the access to relevant amounts of tumor tissue can be limited, and most cases are only diagnosed with Fine Needle Aspirations (FNA) or imaging- and tumor marker-based only. *Adequate tissue for molecular analysis* or novel diagnostics in terms of *liquid biopsies* are necessary for such concepts in LAPC. However, the armamentarium of radiation oncology in terms of physics and biology is ready to face subgroups of patients with *i*RT concepts. Certainly, for some patients, established chemoradiation will remain the best treatment available, while others require local RT dose escalation, and others demand for systemic intensification or immunological interventions.

**Conflicts of interest** None.

## References


1. Gillen S, Schuster T, Meyer Zum BC, Friess H, Kleeff J (2010) Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med 7:e1000267
2. Combs SE, Habermehl D, Werner J, Buchler MW, Debus J (2011) Strategies for preoperative downsizing in patients with local nonresectable pancreatic cancer. Chirurg 82:981–988
3. Combs SE, Ganswindt U, Foote RL, Kondziolka D, Tonn JC (2012) State-of-the-art treatment alternatives for base of skull meningiomas: complementing and controversial indications for neurosurgery, stereotactic and robotic based radiosurgery or modern fractionated radiation techniques. Radiat Oncol 7:226
4. Combs SE, Adeberg S, Dittmar JO, Welzel T, Rieken S, Habermehl D et al (2013) Skull base meningiomas: Long-term results and patient self-reported outcome in 507 patients treated with fractionated stereotactic radiotherapy (FSRT) or intensity modulated radiotherapy (IMRT). Radiother Oncol 106:186–191
5. Combs SE, Welzel T, Schulz-Ertner D, Huber PE, Debus J (2010) Differences in clinical results after LINAC-based single-dose radiosurgery versus fractionated stereotactic radiotherapy for patients with vestibular schwannomas. Int J Radiat Oncol Biol Phys 76: 193–200
6. Combs SE, Thilmann C, Debus J, Schulz-Ertner D (2006) Local radiotherapeutic management of ependymomas with fractionated stereotactic radiotherapy (FSRT). BMC Cancer 6:222
7. Combs SE, Thilmann C, Debus J, Schulz-Ertner D (2006) Long-term outcome of stereotactic radiosurgery (SRS) in patients with acoustic neuromas. Int J Radiat Oncol Biol Phys 64:1341–1347
8. Combs SE, Thilmann C, Edler L, Debus J, Schulz-Ertner D (2005) Efficacy of fractionated stereotactic reirradiation in recurrent gliomas: long-term results in 172 patients treated in a single institution. J Clin Oncol 23:8863–8869
9. Habermehl D, Combs SE (2013) Stereotactic body radiotherapy for the treatment of hepatocellular cancer. Pooled analysis of two phase I/II trials. Strahlenther Onkol 189:1051–1053
10. Combs SE, Herfarth KK, Habermehl D, Debus J (2010) Radiotherapy of hepatic metastases. Chirurg 81:526–532
11. Habermehl D, Herfarth KK, Bermejo JL, Hof H, Rieken S, Kuhn S et al (2013) Single-dose radiosurgical treatment for hepatic metastases—therapeutic outcome of 138 treated lesions from a single institution. Radiat Oncol 8:175
12. Brunner TB, Nestle U, Grosu AL, Partridge M (2015) SBRT in pancreatic cancer: what is the therapeutic window? Radiother Oncol 114:109–116
13. Chang DT, Schellenberg D, Shen J, Kim J, Goodman KA, Fisher GA et al (2009) Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. Cancer 115:665–672
14. Schellenberg D, Kim J, Christman-Skieller C, Chun CL, Columbo LA, Ford JM et al (2011) Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 81:181–188
15. Chuong MD, Springett GM, Freilich JM, Park CK, Weber JM, Mellon EA et al (2013) Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. Int J Radiat Oncol Biol Phys 86:516–522
16. Combs SE, Habermehl D, Kessel K, Bergmann F, Werner J, Brecht I et al (2013) Intensity modulated radiotherapy as neoadjuvant chemoradiation for the treatment of patients with locally advanced pancreatic cancer. Outcome analysis and comparison with a 3D-treated patient cohort. Strahlenther Onkol 189:738–744
17. Bittner MI, Grosu AL, Brunner TB (2015) Comparison of toxicity after IMRT and 3D-conformal radiotherapy for patients with pancreatic cancer - a systematic review. Radiother Oncol 114:117–121
18. Combs SE, Habermehl D, Kessel KA, Bergmann F, Werner J, Naumann P et al (2014) Prognostic impact of CA 19–9 on outcome after neoadjuvant chemoradiation in patients with locally advanced pancreatic cancer. Ann Surg Oncol 21:2801–2807
19. Habermehl D, Kessel K, Welzel T, Hof H, Abdollahi A, Bergmann F et al (2012) Neoadjuvant chemoradiation with Gemcitabine for locally advanced pancreatic cancer. Radiat Oncol 7:28
20. Amano R, Kimura K, Nakata B, Yamazoe S, Motomura H, Yamamoto A et al (2015) Pancreatectomy with major arterial resection after neoadjuvant chemoradiotherapy gemcitabine and S-1 and concurrent radiotherapy for locally advanced unresectable pancreatic cancer. *Surgery 2015 Apr 18*.
21. Andriulli A, Festa V, Botteri E, Valvano MR, Koch M, Bassi C et al (2012) Neoadjuvant/preoperative gemcitabine for patients with localized pancreatic cancer: a meta-analysis of prospective studies. Ann Surg Oncol 19:1644–1662
22. Cho IR, Chung MJ, Bang S, Park SW, Chung JB, Song SY et al (2013) Gemcitabine based neoadjuvant chemoradiotherapy therapy in patients with borderline resectable pancreatic cancer. Pancreatology 13:539–543
23. Evans DB, Varadhachary GR, Crane CH, Sun CC, Lee JE, Pisters PW et al (2008) Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. J Clin Oncol 26:3496–3502
24. Golcher H, Brunner TB, Witzigmann H, Marti L, Bechstein WO, Bruns C et al (2015) Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer: results of the first prospective randomized phase II trial. Strahlenther Onkol 191:7–16
25. Joensuu TK, Kiviluoto T, Karkkainen P, Vento P, Kivisaari L, Tenhunen M et al (2004) Phase I-II trial of twice-weekly gemcitabine and concomitant irradiation in patients undergoing pancreaticoduodenectomy with extended lymphadenectomy for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 60: 444–452
26. Kunzmann V, Herrmann K, Bluemel C, Kapp M, Hartlapp I, Steger U (2014) Intensified neoadjuvant chemotherapy with Nab-paclitaxel plus gemcitabine followed by FOLFIRINOX in a patient with locally advanced unresectable pancreatic cancer. Case Rep Oncol 7:648–655
27. Landry J, Catalano PJ, Staley C, Harris W, Hoffman J, Talamonti M et al (2010) Randomized phase II study of gemcitabine plus radiotherapy versus gemcitabine, 5-fluorouracil, and cisplatin followed by radiotherapy and 5-fluorouracil for patients with locally

advanced, potentially resectable pancreatic adenocarcinoma. J Surg Oncol 101:587–592
28. Leone F, Gatti M, Massucco P, Colombi F, Sperti E, Campanella D et al (2013) Induction gemcitabine and oxaliplatin therapy followed by a twice-weekly infusion of gemcitabine and concurrent external-beam radiation for neoadjuvant treatment of locally advanced pancreatic cancer: a single institutional experience. Cancer 119:277–284
29. Varadhachary GR, Wolff RA, Crane CH, Sun CC, Lee JE, Pisters PW et al (2008) Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. J Clin Oncol 26:3487–3495
30. Watanabe F, Honda G, Kurata M, Tsuruta K, Tokashiki T, Funada N (2009) A case report-neoadjuvant chemoradiotherapy with combination of S-1 and gemcitabine in a patient with locally advanced pancreatic cancer. Gan To Kagaku Ryoho 36:2430–2432
31. Sho M, Akahori T, Tanaka T, Kinoshita S, Nagai M, Nishiwada S et al (2015) Optimal indication of neoadjuvant chemoradiotherapy for pancreatic cancer. *Langenbecks Arch Surg*
32. Roland CL, Yang AD, Katz MH, Chatterjee D, Wang H, Lin H et al (2015) Neoadjuvant therapy is associated with a reduced lymph node ratio in patients with potentially resectable pancreatic cancer. Ann Surg Oncol 22:1168–1175
33. Bertocchi P, Abeni C, Meriggi F, Rota L, Rizzi A, Di Biasi B et al (2015) Gemcitabine Plus Nab-Paclitaxel as Second-Line and Beyond Treatment for Metastatic Pancreatic Cancer: a Single Institution Retrospective Analysis. *Rev Recent Clin Trials*
34. Hosein PJ, de Lima LG Jr, Pastorini VH, Gomez C, Macintyre J, Zayas G et al (2013) A phase II trial of nab-paclitaxel as second-line therapy in patients with advanced pancreatic cancer. Am J Clin Oncol 36:151–156
35. Lo RG, Santeufemia DA, Foltran L, Bidoli E, Basso SM, Lumachi F (2015) Prognostic factors of survival in patients treated with nab-paclitaxel plus gemcitabine regimen for advanced or metastatic pancreatic cancer: a single institutional experience. Oncotarget 6:8255–8260
36. Olowokure O, Torregroza-Sanchez MP, Bedoya-Apraez ID (2013) Gemcitabine plus Nab-paclitaxel with chemoradiation in locally advanced pancreatic cancer (LAPC). J Gastrointest Oncol 4:E16–E18
37. Tabernero J, Chiorean EG, Infante JR, Hingorani SR, Ganju V, Weekes C et al (2015) Prognostic factors of survival in a randomized phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic pancreatic cancer. Oncologist 20:143–150
38. Vogel A, Pelzer U, Salah-Eddin AB, Koster W (2014) First-line nab-paclitaxel and gemcitabine in patients with metastatic pancreatic cancer from routine clinical practice. In Vivo 28:1135–1140
39. Von Hoff DD, Ramanathan RK, Borad MJ, Laheru DA, Smith LS, Wood TE et al (2011) Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. J Clin Oncol 29:4548–4554
40. Blazer M, Wu C, Goldberg RM, Phillips G, Schmidt C, Muscarella P et al (2015) Neoadjuvant modified (m) FOLFIRINOX for locally advanced unresectable (LAPC) and borderline resectable (BRPC) adenocarcinoma of the pancreas. Ann Surg Oncol 22:1153–1159
41. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y et al (2011) FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817–1825
42. Gunturu KS, Yao X, Cong X, Thumar JR, Hochster HS, Stein SM et al (2013) FOLFIRINOX for locally advanced and metastatic pancreatic cancer: single institution retrospective review of efficacy and toxicity. Med Oncol 30:361
43. Hosein PJ, Macintyre J, Kawamura C, Maldonado JC, Ernani V, Loaiza-Bonilla A et al (2012) A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. BMC Cancer 12:199
44. Marthey L, Sa-Cunha A, Blanc JF, Gauthier M, Cueff A, Francois E et al (2015) FOLFIRINOX for locally advanced pancreatic adenocarcinoma: results of an AGEO multicenter prospective observational cohort. Ann Surg Oncol 22:295–301
45. Moorcraft SY, Khan K, Peckitt C, Watkins D, Rao S, Cunningham D et al (2014) FOLFIRINOX for locally advanced or metastatic pancreatic ductal adenocarcinoma: the royal marsden experience. Clin Colorectal Cancer 13:232–238
46. Peddi PF, Lubner S, McWilliams R, Tan BR, Picus J, Sorscher SM et al (2012) Multi-institutional experience with FOLFIRINOX in pancreatic adenocarcinoma. JOP 13:497–501
47. Naumann P, Habermehl D, Welzel T, Debus J, Combs SE (2013) Outcome after neoadjuvant chemoradiation and correlation with nutritional status in patients with locally advanced pancreatic cancer. Strahlenther Onkol 189:745–752
48. Ferrucci LM, Bell D, Thornton J, Black G, McCorkle R, Heimburger DC et al (2011) Nutritional status of patients with locally advanced pancreatic cancer: a pilot study. Support Care Cancer 19:1729–1734
49. Bachmann J, Heiligensetzer M, Krakowski-Roosen H, Buchler MW, Friess H, Martignoni ME (2008) Cachexia worsens prognosis in patients with resectable pancreatic cancer. J Gastrointest Surg 12:1193–1201
50. Wang X, Hu Z, Hu J, Du J, Mitch WE (2006) Insulin resistance accelerates muscle protein degradation: activation of the ubiquitin-proteasome pathway by defects in muscle cell signaling. Endocrinology 147:4160–4168
51. Di Sebastiano KM, Yang L, Zbuk K, Wong RK, Chow T, Koff D et al (2013) Accelerated muscle and adipose tissue loss may predict survival in pancreatic cancer patients: the relationship with diabetes and anaemia. Br J Nutr 109:302–312
52. Montgomery RC, Hoffman JP, Riley LB, Rogatko A, Ridge JA, Eisenberg BL (1997) Prediction of recurrence and survival by post-resection CA 19–9 values in patients with adenocarcinoma of the pancreas. Ann Surg Oncol 4:551–556
53. Kondo N, Murakami Y, Uemura K, Hayashidani Y, Sudo T, Hashimoto Y et al (2010) Prognostic impact of perioperative serum CA 19–9 levels in patients with resectable pancreatic cancer. Ann Surg Oncol 17:2321–2329
54. Kinsella TJ, Seo Y, Willis J, Stellato TA, Siegel CT, Harpp D et al (2008) The impact of resection margin status and postoperative CA19-9 levels on survival and patterns of recurrence after postoperative high-dose radiotherapy with 5-FU-based concurrent chemotherapy for resectable pancreatic cancer. Am J Clin Oncol 31:446–453
55. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K et al (2007) Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA 297:267–277
56. Liu P, Zhu Y, Liu L (2015) Elevated serum CA72-4 levels predict poor prognosis in pancreatic adenocarcinoma after intensity-modulated radiation therapy. Oncotarget 6:9592–9599
57. Kim H, Saka B, Knight S, Borges M, Childs E, Klein A et al (2014) Having pancreatic cancer with tumoral loss of ATM and normal TP53 protein expression is associated with a poorer prognosis. Clin Cancer Res 20:1865–1872
58. Gundewar C, Sasor A, Hilmersson KS, Andersson R, Ansari D (2015) The role of SPARC expression in pancreatic cancer progression and patient survival. *Scand J Gastroenterol* 1–5
59. Mantoni TS, Schendel RR, Rodel F, Niedobitek G, Al Assar O, Masamune A et al (2008) Stromal SPARC expression and patient survival after chemoradiation for non-resectable pancreatic adenocarcinoma. Cancer Biol Ther 7:1806–1815

60. Sinn M, Sinn BV, Striefler JK, Lindner JL, Stieler JM, Lohneis P et al (2014) SPARC expression in resected pancreatic cancer patients treated with gemcitabine: results from the CONKO-001 study. Ann Oncol 25:1025–1032
61. Aref A, Berri R (2012) Role of radiation therapy in the management of locally advanced pancreatic cancer. J Clin Oncol 30:1564–1565
62. Bachet JB, Marechal R, Demetter P, Bonnetain F, Couvelard A, Svrcek M et al (2012) Contribution of CXCR4 and SMAD4 in predicting disease progression pattern and benefit from adjuvant chemotherapy in resected pancreatic adenocarcinoma. Ann Oncol 23:2327–2335
63. Blackford A, Serrano OK, Wolfgang CL, Parmigiani G, Jones S, Zhang X et al (2009) SMAD4 gene mutations are associated with poor prognosis in pancreatic cancer. Clin Cancer Res 15:4674–4679
64. Crane CH, Varadhachary GR, Yordy JS, Staerkel GA, Javle MM, Safran H et al (2011) Phase II trial of cetuximab, gemcitabine, and oxaliplatin followed by chemoradiation with cetuximab for locally advanced (T4) pancreatic adenocarcinoma: correlation of Smad4(Dpc4) immunostaining with pattern of disease progression. J Clin Oncol 29:3037–3043
65. Singh P, Srinivasan R, Wig JD (2012) SMAD4 genetic alterations predict a worse prognosis in patients with pancreatic ductal adenocarcinoma. Pancreas 41:541–546
66. Yamada S, Fujii T, Shimoyama Y, Kanda M, Nakayama G, Sugimoto H et al (2015) SMAD4 expression predicts local spread and treatment failure in resected pancreatic cancer. Pancreas 44: 660–664
67. Greenhalf W, Ghaneh P, Neoptolemos JP, Palmer DH, Cox TF, Lamb RF et al (2014) Pancreatic cancer hENT1 expression and survival from gemcitabine in patients from the ESPAC-3 trial. J Natl Cancer Inst 106:djt347
68. Nordh S, Ansari D, Andersson R (2014) hENT1 expression is predictive of gemcitabine outcome in pancreatic cancer: a systematic review. World J Gastroenterol 20:8482–8490
69. Knaebel HP, Marten A, Schmidt J, Hoffmann K, Seiler C, Lindel K et al (2005) Phase III trial of postoperative cisplatin, interferon alpha-2b, and 5-FU combined with external radiation treatment versus 5-FU alone for patients with resected pancreatic adenocarcinoma—CapRI: study protocol [ISRCTN62866759]. BMC Cancer 5:37
70. Marten A, Schmidt J, Ose J, Harig S, Abel U, Munter MW et al (2009) A randomized multicentre phase II trial comparing adjuvant therapy in patients with interferon alpha-2b and 5-FU alone or in combination with either external radiation treatment and cisplatin (CapRI) or radiation alone regarding event-free survival - CapRI-2. BMC Cancer 9:160
71. Schmidt J, Jager D, Hoffmann K, Buchler MW, Marten A (2007) Impact of interferon-alpha in combined chemoradioimmunotherapy for pancreatic adenocarcinoma (CapRI): first data from the immunomonitoring. J Immunother 30:108–115
72. Schmidt J, Patrut EM, Ma J, Jager D, Knaebel HP, Buchler MW et al (2006) Immunomodulatory impact of interferon-alpha in combination with chemoradiation of pancreatic adenocarcinoma (CapRI). Cancer Immunol Immunother 55:1396–1405
73. Mizukami T, Kamachi H, Mitsuhashi T, Tsuruga Y, Hatanaka Y, Kamiyama T et al (2014) Immunohistochemical analysis of cancer stem cell markers in pancreatic adenocarcinoma patients after neoadjuvant chemoradiotherapy. BMC Cancer 14:687
74. Rasheed ZA, Yang J, Wang Q, Kowalski J, Freed I, Murter C et al (2010) Prognostic significance of tumorigenic cells with mesenchymal features in pancreatic adenocarcinoma. J Natl Cancer Inst 102:340–351
75. Kahlert C, Bergmann F, Beck J, Welsch T, Mogler C, Herpel E et al (2011) Low expression of aldehyde dehydrogenase 1A1 (ALDH1A1) is a prognostic marker for poor survival in pancreatic cancer. BMC Cancer 11:275
76. Combs SE, Schulz-Ertner D, Herfarth KK, Krempien R, Debus J (2006) Advances in radio-oncology. From precision radiotherapy with photons to ion therapy with protons and carbon ions. Chirurg 77:1126–1132
77. Kessel KA, Jager A, Habermehl D, Ruppell J, Bendl R, Debus J et al (2015) Changes in Gross Tumor Volume and Organ Motion Analysis During Neoadjuvant Radiochemotherapy in Patients With Locally Advanced Pancreatic Cancer Using an In-House Analysis System. *Technol Cancer Res Treat*
78. Habermehl D, Henkner K, Ecker S, Jakel O, Debus J, Combs SE (2013) Evaluation of different fiducial markers for image-guided radiotherapy and particle therapy. J Radiat Res 54(Suppl 1):i61–i68
79. Richter D, Graeff C, Jakel O, Combs SE, Durante M, Bert C (2014) Residual motion mitigation in scanned carbon ion beam therapy of liver tumors using enlarged pencil beam overlap. Radiother Oncol 113:290–295
80. Richter D, Saito N, Chaudhri N, Hartig M, Ellerbrock M, Jakel O et al (2014) Four-dimensional patient dose reconstruction for scanned ion beam therapy of moving liver tumors. Int J Radiat Oncol Biol Phys 89:175–181
81. El Shafie RA, Habermehl D, Rieken S, Mairani A, Orschiedt L, Brons S et al (2013) In vitro evaluation of photon and raster-scanned carbon ion radiotherapy in combination with gemcitabine in pancreatic cancer cell lines. J Radiat Res 54(Suppl 1):i113–i119
82. Engelsman M, DeLaney TF, Hong TS (2011) Proton radiotherapy: the biological effect of treating alternating subsets of fields for different treatment fractions. Int J Radiat Oncol Biol Phys 79:616–622
83. Kozak KR, Kachnic LA, Adams J, Crowley EM, Alexander BM, Mamon HJ et al (2007) Dosimetric feasibility of hypofractionated proton radiotherapy for neoadjuvant pancreatic cancer treatment. Int J Radiat Oncol Biol Phys 68:1557–1566
84. Ling TC, Slater JM, Mifflin R, Nookala P, Grove R, Ly AM et al (2015) Evaluation of normal tissue exposure in patients receiving radiotherapy for pancreatic cancer based on RTOG 0848. J Gastrointest Oncol 6:108–114
85. Hoppe BS, Mamalui-Hunter M, Mendenhall NP, Li Z, Indelicato DJ (2013) Improving the therapeutic ratio by using proton therapy in patients with stage I or II seminoma. Am J Clin Oncol 36:31–37
86. Lee RY, Nichols RC Jr, Huh SN, Ho MW, Li Z, Zaiden R et al (2013) Proton therapy may allow for comprehensive elective nodal coverage for patients receiving neoadjuvant radiotherapy for localized pancreatic head cancers. J Gastrointest Oncol 4:374–379
87. Nichols RC Jr, George TJ, Zaiden RA Jr, Awad ZT, Asbun HJ, Huh S et al (2013) Proton therapy with concomitant capecitabine for pancreatic and ampullary cancers is associated with a low incidence of gastrointestinal toxicity. Acta Oncol 52:498–505
88. Terashima K, Demizu Y, Hashimoto N, Jin D, Mima M, Fujii O et al (2012) A phase I/II study of gemcitabine-concurrent proton radiotherapy for locally advanced pancreatic cancer without distant metastasis. Radiother Oncol 103:25–31
89. Hong TS, Ryan DP, Borger DR, Blaszkowsky LS, Yeap BY, Ancukiewicz M et al (2014) A phase 1/2 and biomarker study of preoperative short course chemoradiation with proton beam therapy and capecitabine followed by early surgery for resectable pancreatic ductal adenocarcinoma. Int J Radiat Oncol Biol Phys 89:830–838