The Role of Radiotherapy in Pancreatic Cancer

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The radiotherapy role in pancreatic cancer is under debate. The most relevant studies were reviewed trying to draw a conclusion regarding the role of the radiotherapy in the management of pancreatic cancer.

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Pancreatic cancer is the fourth leading cause of cancer death in the US and in the European Union. Although only the 9th most common cancer, it is an advanced disease at presentation, with only 10-15% of patients having surgically resectable disease, 30% advanced non-resectable cancer and 50% metastatic carcinoma (1), the corresponding figures for survival being 15-19 months, 6-10 months and 3 to 6 months respectively (2).

The role of radiotherapy (RT) for patients with pancreatic cancer is controversial because of the premise that patients die as a result of distant metastasis. Autopsy studies have shown that one third of deaths in patients with pancreatic cancer were due to local progression, without evidence of distant metastasis, and 70% were due to distant metastasis, some with both local and distant disease (3-5). Systemic chemotherapy (CT) remains the gold standard for metastatic patients with good performance status. Adjuvant CT after resection (CH) of localized and locally advanced disease has been found to improve outcome. In particular, gemcitabine based combined CT leads to an improvement in overall survival (6). RT should always be performed as radiochemotherapy (RCT), except for the rare cases of palliative treatment of bone metastases. Two randomized trials have compared treatment with RT alone to combined RCT for unresectable pancreatic carcinoma. RT alone demonstrated a worse median survival than RCT in the Mayo Clinic study (6 versus 10 months) (7).

These results were confirmed by GITSG (Gastro Intestinal Study Group) 92-73 trial (8).

RT can be used in the adjuvant setting, after CH, to reduce loco-regional relapses or in the neoadjuvant setting to reduce locally advanced tumors and obtain more R0- resections, correlated with better local control and overall survival. In unresectable disease RT plays a palliative role or, in some cases, to obtain better survival when combined with neoadjuvant and adjuvant CT.

Adjuvant radiochemotherapy

The relatively high rate of both locoregional and distant recurrence following CH makes a strong case for effective adjuvant therapy. Randomized studies relative to the role of RCT are limited, with available data derived from some phase II and single Institution studies. The first prospective multicenter study was the small GISTG 91-73 trial (9) in which 43 patients with resectable cancer were randomized to CH followed by RCT, 40 Gy split course, with concurrent 5-FU, followed by maintenance 5-FU for 2 years or until progression vs. CH alone. The combined treatment evidenced better overall survival (43% vs. 18% at 2 years and 14% vs. 5 % at 5 years). The study was updated with 32 non randomized patients enrolled into the adjuvant therapy group, with 2 year overall survival of 46% (10). Following this trial adjuvant RCT became the standard of care in the U. S. However the study has been criticized for its poor accrual, low statistical power, suboptimal RT schedule, lack of RT quality assurance and non compliance with maintenance CT in 75% of patients.

The European Organization for Research and Treatment of Cancer conducted a similar study in Europe (EORTC 40891) (11): 281 patients with resectable pancreatic or periampullary cancer were ran-
domized to RCT: 40 Gy split course with concomitant 5-FU delivered as an infusion and no maintenance CT vs observation (OBS). The adjuvant treatment failed to demonstrate a significantly better 2 year progression free survival or overall survival. The criticisms of this study are: only 119 patients had pancreatic cancer; they did not receive a maintenance therapy; positive and negative margins without stratification were included and the quality assurance of the RT in this trial was missing.

The European Study Group for Pancreatic Cancer (ESPAC-1 trial) (12), conducted the largest phase III study between 1999 and 2000. Five hundred and forty one patients with pancreatic or periampullary cancer were included, but not all randomized to receive:

a) CT vs OBS, b) RCT vs OBS and c) a 2x2 factorial design- arms of OBS vs CT (5-FU/leucovorin) vs RCT: 40 Gy split course with bolus 5- FU +/- maintenance CT.

For all patients, CT had significantly improved median survival, while for randomized patients only, CT had no effect on median survival, thus yielding contradictory results. RCT, both for all and for randomized patients, did not significantly affect median survival. The final results were published after 3 years (13), with 47 months of median follow up. The authors concluded that CT was of benefit, while RCT was detrimental, but only 128 patients had RT details available and only 90 reached the prescribed dose of 40 Gy. Again the trial was criticized because of the suboptimal RT, the use of a split course technique, prolonged treatment time and the very poor rate of tumor control. The split course treatment is considered suboptimal by current standards due to the risk of accelerated repopulation of tumor cells during the split period (14). The total dose was low (40 Gy), and the 5-FU was given in a bolus injection, known to be inferior to prolonged intravenous infusional schedules. The patients were treated with parallel opposed anterior-posterior simple fields, a technique leading to significant treatment side effects. Progressive disease in 19% of patients precluded RT. Wide variation in the RT doses employed and the allowance of background therapy with CT and RCT prior to randomization could all have potentially influenced the final analysis. The RTOG 97-04 study (15) used higher doses (50.4 Gy) of continuous irradiation, comparing two different chemotherapy regimens: 5-FU in continuous infusion vs. 5-FU plus gemcitabine pre and postRCT. Four hundred and forty two patients were treated with modern RT techniques, and prospective quality assurance was requested. The gemcitabine arm patients had better median overall survival results in pancreatic head tumors (20.6 vs 16.9 months, p= 0.033), with a higher hematological G4 toxicity, but without a difference in the rate of febrile neutropenia. This study changed the standard adjuvant therapy for NCI and NCCN (16).

RTOG 97-04 included patients with more unfavorable distribution of risk factors (R1, N+ and larger T dimensions) compared with the previous ESPAC -1 trial and the CONKO-001 trial, which compared CT alone with OBS after the CH (17). The local recurrence rates were 25% in the RTOG trial, 47% in GITSG trial and 62% overall in ESPAC trial. Despite a double rate of positive margin compared with the CONKO-001 trial, local control was better (25 vs 38% in both arms, 34% with and 41% without gemcitabine). The superior quality and technique of RCT may explain this difference, and it can be hypothesized that effective RT could enhance the treatment results (16).

Conflicting conclusions resulted from two of the last meta-analyses published: those of Stocken (18) because of the predominance of the ESPAC-1 patients in its meta-analysis, and those of Khanna (19) because of the inclusion of a non randomized study by Yeo et al (20). In the Khanna report a relative weight was taken into account and he calculated an absolute gain in survival from adjuvant RCT of 12% after 2 years(p= 0.011, 95% CI, 3-21%) as the result of five randomized trials comparing CH with RCT. Stocken concluded that adjuvant RCT is more effective than CT only after R1-resections, with a reduction of the hazard ratio of 28% (std dev 19).

The value of adjuvant RCT is currently controversial, with different interpretations on either sides of the Atlantic. RCT represents the standard of care in North America, while in Europe adjuvant CT alone could be indicated after R0-resection, and RCT after R1-resection.

**Neoadjuvant radiochemotherapy**

The neoadjuvant RCT concept has the same rationale as in other tumor localizations: any partial response to treatment reduces the tumor volume, potentially increasing the likelihood of a negative margin at CH. The resected tumor can serve as its own biological "marker" of treatment response. In addition, the undisturbed tumor microenvironment, permitting better oxygenation of tumor tissue, may enhance treatment effects. Hypoxia is in fact one of the most important factors affecting radiation resistance. Finally, multimodality therapy is likely to be better tolerated prior to, rather than after, a radical pancreateicoduodenectomy. Many patients did not recover within 6 to 8 weeks after surgery, and could not receive the RCT according the op-
timal timing (15). Patients who develop unresectable or metastatic disease during the induction treatment phase are also spared the morbidity of such a radical procedure, as demonstrated by ESPAC-1 and CONKO-001 trial (12, 17).

Thus, neoadjuvant RCT should be considered for patients with borderline resectable disease as determined through a complete clinical staging.

No prospective phase III randomized study were published regarding neoadjuvant RCT.

A prospective comparative study at Mount Sinai Hospital (NY) (21) gave surprising results: 91 resectable patients underwent pancreaticoduodenectomy, followed in 63 cases by adjuvant RT or CT, and reached a median overall survival of 14 months (low if compared with other modern studies). In the same Institution 68 non-resectable patients were treated with split-course RT to a total dose of 54 Gy and concomitant 5-FU, Streptozotocin and Cisplatin. Thirty of 68 patients with initially unresectable tumor underwent CH after more than 10 weeks, with downstaging observed in 20 patients. The median overall survival was 23.6 months (p= 0.006) in the surgical patients and 18 months in non operated patients. This is probably due to the fact that the CT was continued after the RT. Delayed response on CT scan after RCT has often been reported, and repeated reassessment of resectability could have increased CH rates in this trial. It is not clear to what degree split course RT has contributed to the results.

In another study, at the MD Anderson Cancer Center (22), 86 patients were treated with neoadjuvant RCT to a total dose of 30 Gy, with concurrent gemcitabine. Eleven-twelve weeks later CH was performed and 74% of the patients had tumor resection, a better result than in their previous studies using 5-FU (23). In 58% of the resected tumors a pathological response higher than 50% was registered and the median overall survival was 36 months.

At the Duke University Medical Center 111 non metastatic pancreatic tumor patients were treated with RCT to a total dose of 45 Gy plus 5.4 Gy boost, with 5-FU/Mitomicin/ Cisplatin chemotherapy: 72% of the patients had R0 resection and 70% were ypN0, with a survival rate of 32% at 2 years (24).

A meta-analysis of the neoadjuvant treatments (94% RCT and 6% CT only) on more than 4000 patients, demonstrated that the non resectable patients treated with neoadjuvant therapies can reach survival comparable to those with initially resectable tumor (median overall survival 20.5 vs 23.3 months) (25).

No conclusions could be reached prior to the results of the ongoing first randomized multicenter study of the Interdisciplinary Working Group Gastrointestinal Tumours (26). Neoadjuvant therapy is expected to prolong survival by achieving higher rates of curative resections (R0), ypN0 tumors, and to increase local tumor control. Patients with locally advanced, unresectable tumors could, in 20% of cases, reach resectability after the neoadjuvant RCT.

Finally, “ borderline resectable” patients, those with abutment or encasement of portal vein, superior mesenteric vein, or superior mesenteric artery less than or equal to 180° or short segment (less than or equal to 1.5 cm), encasement of the superior mesenteric vein or portal vein which is amenable to partial resection of the vein and reconstruction, are more likely to have R1 or R2 resections, and hence a neoadjuvant strategy could be employed to increase the prospect of an R0 resection.

Radical treatments in locally advanced tumors

At the time of diagnosis, locally advanced pancreatic cancer is presented by one third of patients, that is those with real unresectable disease in absence of distant metastases. The optimal treatment in these cases is currently under debate; the chance for a cure is low with RT alone. Combination with chemotherapy is logical : Shinchi et al (27) demonstrated in 31 patients with locally advanced pancreatic cancer that RCT(50.4 Gy plus concurrent and maintenance 5-FU) versus best supportive care, obtain better median survival (13.2 months vs 6.4 months) and better quality of life, but can be associated with significant toxicity.

The GITSG study 92-73(8) on 194 patients with unresectable pancreatic cancer, randomized in three arms: split course RT to a total dose of 40 Gy with concomitant bolus of 5-FU vs split course RT to a total dose of 60 Gy with concomitant bolus of 5-FU versus RT to a total dose of 60 Gy alone, confirmed the earlier Mayo Clinic results (7), with both concomitant CT arms reaching prolonged median survival(42.2 weeks, versus 40.3 weeks, versus 22.9 weeks). This trial also raised the possibility that, with CT, a higher dose of radiation is perhaps not necessary because the 1 year survival rates were similar in the 60 Gy and 40 Gy arms.

Previous randomized phase II studies comparing RCT with CT showed some superiority of RCT in terms of local control and OS (28-30). However, a recent phase III trial reported inferior results with the combined treatment (31). The RT dose used in these studies was suboptimal, of only 40 Gy. RT techniques were also outdated in both ‘80s studies, because most patients were treated with parallel opposed anterior and posterior portals, associated with higher rates of toxic-
ity, and CT-based imaging was not required for the treatment planning, which could have resulted in significant geographical misses. It is obvious that the meta-analysis, including these reports, did not provide a definitive answer (32).

The ECOG 4201 study used the modern radiotherapy techniques (33). Thirty six patients treated with gemcitabine and RT were compared with 38 patients treated with gemcitabine alone. Overall survival was better in the combined modality treatment (median overall survival 11 vs 9.2 months, p= 0.034; 50% vs 32% at 12 months, 29 vs 11% at 18 months and 12 vs 4% at 24 months), but with increased toxicity, probably deriving from the high dose of gemcitabine used (600 mg/mq). Combinations of RCT and neoadjuvant or adjuvant CT reported median overall survival of 13-15 months, but this approach is currently under investigation by the LAP07 trial (34,35).

Considering that the majority of patients with locally advanced disease recur at distant sites, the concept of induction CT was developed to improve prognosis in this group. This strategy could allow the selection of patients who will benefit most from RT. Patients who develop distant metastases during induction CT continue with CT alone.

At the MD Anderson Cancer Center a retrospective analysis showed that 73 patients receiving induction CT for 2.5 months before RCT had a significantly longer survival compared with 245 patients receiving RCT as first treatment (36). In a recently published nonrandomized series (37) 181 patients were treated with gemcitabine – based CT for 3 months and those with stable disease(128 pts) were treated with RCT or CT alone. The median survival time was significantly longer(15 versus 11.7 months) in patients who underwent RCT. This result is probably due to the stable disease obtained with induction CT.

These data are promising but there is a clear need for a well designed study to test this hypothesis.

In our Department we currently use induction CT, followed by RCT. The experience acquired by our department in advanced pancreatic cancer is summarized in two studies published as abstracts in Int J Radiat Oncol Biol Phys, in 2009 and 2010. The first was a phase I study on 29 patients with a median age of 60 years (38). Thirty three patients were stage III; 3 were stage IV and 3 were local relapse patients. The patients underwent 4D contrast enhanced CT simulation after neoadjuvant CT. A total dose of 44.25 Gy in 15 fractions was prescribed to PTV1 (whole tumor) on 13 patients and in 16 patients a dose escalation with simultaneous integrated boost (SIB) from 48 to 55 Gy was prescribed to PTV 2 (a tumor subvolume of 1 cm around the infiltrated vessels). Concomitant CT with 5 FU iv or Capecitabine was given. With only two patients presenting G3 toxicity (7%), the SIB to infiltrating vessels did not improve the response rate.

A phase II study was published as an abstract in 2010 (39). From June 2006 to November 2009, 33 patients with pancreatic adenocarcinoma were treated with hypofractionated helical tomotherapy (TomoTherapy Hi-Art II, Madison) and concomitant oral capecitabine. They had a median age of 62 years and comprised 19 women and 14 men, 24 being in the IIId stage and 9 in IVth stage, with controlled metastatic disease. Thirty patients received a neoadjuvant chemotherapy. The patients were simulated with 4D contrast enhanced CT or FDG-PET/CT. The dose delivered to PTV was 44.25 Gy/15 fractions with 1250 mg/mq/day concomitant oral Capecitabine. With an acceptable rate of G3 toxicity (1 patient with diarrhea and 1 patient with gastric ulcer) 3 patients presented PR(10%), 22 SD(80%) and only 3 patients PD(10%). The median time to progression was 14.5 months, the median time to local progression was 10.3 months and the 18 month overall survival was 63%, showing that the RCT treatment, after neoadjuvant CT, could enhance the long term outcome of advanced pancreatic tumor patients.

To summarize, it is difficult to define the role of RCT in locally advanced disease. The most important arguments for RCT are the 10-20% rate of secondary resectability, which has not been reported with CT alone, and the evidence of better results than with best supportive care. In borderline tumors long term survival as high as 40 months has been reported with neoadjuvant RCT followed by CH (40).

Future prospects

Promising results have been reported using TNFerade™ with RCT. TNFerade™ is a replication deficient adenoviral vector containing the radiation-inducible EGR-1 gene promoter of TNF factor complementary DNA and in one study it was added to a continuous infusion of 5- FU and RT to a total dose of 50.4 Gy, and compared to 5-FU and RT alone. 1 year survival was 70.5% in the TNFerade arm, versus 28% in the standard treatment arm (41).

A phase I trial of oral nelfinavir, an HIV protease inhibitor with radiosensitizing activity in vitro and in vivo, started 3 days before and concurrent with 50.4-59.4 Gy RT and gemcitabine, showing acceptable toxicity and promising activity (42). Ten out of 12 patients completed the treatment, five had partial responses on CT scans and 5 complete responses on PET/CT scans. Six patients had R0 resection, with one ypT0. This sec-
ondary complete resection rate is superior to the 15-20% reported in other similar series, suggesting an enhanced local tumor response with nelfinavir.

**Radiotherapy technique and side effects**

When RT techniques are complex, as in pancreatic carcinoma, problems with the quality of the delivered RT are more likely. Quality assurance in RT for pancreatic cancer should comprise standard dosimetry assessment, adequate PTV coverage and adequate sparing of normal surrounding tissues. Treatment planning should be 3D conformal and IMRT is recommended. Total dose could be escalated up to over 60 Gy using multiple field techniques or IMRT together with restrictive target volume definition (43). Radiation volume has been shown to correlate with gastrointestinal toxicity in patients treated with concurrent gemcitabine, a potent radiosensitizer in radiobiological models. The total treated volume, even with elective nodal irradiation, should be below 600 ml, because tolerance of gemcitabine concomitant treatment is dependent on the total volume (44). There is no consensus on the regional lymphatic nodal irradiation. It is known that more than 80% of all resectable pancreatic head carcinomas have regional lymph nodes metastases, but most of these regions are probably within the 80% isodose volume even if elective nodal irradiation is not prescribed, as shown by Murphy and colleagues (45). The omission lymph node coverage did not compromise the freedom from local progression in this study and, notably, local failure correlated with increased mortality, independent of distant metastases.

Conventional radiotherapy should be delivered with a total dose of 50-55 Gy, with the exception of controlled trials. The critical organs dose limits are:

- Liver: 100% of the volume < 20 Gy, 70% of the volume < 30 Gy, median dose < 24-27 Gy.
- Stomach and intestine, which tolerates doses up to 50 Gy on small volumes
  - Kidneys: ≤ 50% of one kidney > 20 Gy and the other kidney ≤ 30% at > 20 Gy.
  - Spine: ≤ 45% maximal dose.

During RCT 95% of the patients experienced at least one of the following symptoms: increased severe fatigue, nausea, sleep disorder, loss of appetite, pain and impaired sense of overall well-being (46). Weight loss is very common among patients with pancreatic cancer. Supportive therapies during RCT are very important, because weight stabilization in unresectable cancer was associated with improved quality of life and survival, with a difference of 3 months (47).

In order to reduce the toxicity associated with RT to the pancreas newer techniques have been employed which are aimed at excluding as much normal tissue as feasible, and thereby escalating the dose to influence local control and, ultimately, survival.

IORT has the advantage of delivering RT to the tumor/tumor bed under direct vision and reducing toxicity by shielding dose-limiting normal tissues. Methods of IORT include either implantation of iodine-125 seeds or intraoperative electron beam RT-IOERT. A trial by the National Cancer Institute showed better local control with 20 Gy of IORT following surgical therapy than with observation alone. For 150 patients treated with IORT and 5-FU based CT, Massachusetts General Hospital reported a 7% 3 year survival, and 5 of 150 patients survived for more than 5 years (48,49).

Stereotactic RT (SRT) aims to deliver one to five high dose fractions to the area of the gross tumor. The advantage could be the possibility to deliver a high dose only to the target, adding conventional RT to treat the risk area around the tumor. The Stanford group used a single fraction of 25 Gy, obtaining 81% local control (50). The same group studied the association of SRT as a boost to external beam RT, yielding 84% local control with unacceptable toxicity: 12.5% rate of late duodenal ulceration. No improvement in median survival time was noted in any of these studies. Chang and colleagues reported their results with stereotactic RT on 77 patients, of whom 81% had locally advanced pancreatic cancer. They were treated with a single fraction of 25 Gy and 84% of patients were free for local progression at 12 months. In locally advanced disease, median survival was only 6.7 months, and the systemic therapy was not defined (51).

Intensity Modulated RT (IMRT) is delivered as conformal RT but with varying intensities within each radiation field. This has the advantage of mapping the dose to obtain a high dose to the tumor volume and at the same time an optimal sparing of normal surrounding tissues. Preliminary results reported in the Ben-Josef study using dose escalation IMRT are promising, with median overall survival of 23.1 months and only 1 case(4%) of local progression for a total dose from 50 to 60 Gy given over 5 weeks (52). With superior planning technique and effective monitoring of toxicity IMRT seems to be safe even if associated with concomitant CT.

Radiation dose escalation could be obtained easier using modern IMRT and IGRT techniques that reach better dose distribution (Fig. 1, 2, 3, 4). In fact our institutional studies, with hypofractionated dose escalation are based on the very precise IGRT treatments with helical tomotherapy.
Fig. 1: Dose distribution with 3DCRT.

Fig. 2: Dose distribution with helical Tomotherapy.

Fig. 3: Dose distribution with rapid arc.
Fig. 4: IGRT with helical tomotherapy (Hi-Art II, Madison).

References:

23. Pisters PW, Abbruzzese JL, Janjan NA et al. Rapid-fractionation preoperative chemoradiation, pancreaticoduodenectomy and in-


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