# INTENSITY-MODULATED RADIOTHERAPY IN THE TREATMENT OF PANCREATIC ADENOCARCINOMA: A REVIEW

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## ABSTRACT

Pancreatic cancer remains one of the leading causes of cancer deaths. Despite improvements in imaging, surgical techniques, chemotherapy agents, and radiation techniques, the prognosis for patients with pancreatic adenocarcinoma remains poor. Traditionally, radiotherapy (RT) has been utilised as neoadjuvant, adjuvant, or definitive treatment, and represents an important therapeutic option in pancreatic adenocarcinoma. Intensity-modulated radiation therapy (IMRT), a more recent RT technique, has the potential to deliver an adequate dose to the tumour volume with a minimal dose to the surrounding critical structures such as duodenum, small intestine, liver, kidneys, and spinal cord. This article provides a review about the role of IMRT in the treatment of pancreatic cancer, concerning clinical outcomes such as toxicity, local control, and overall survival.

Keywords: Pancreatic cancer, intensity-modulated radiotherapy, toxicity, outcome.

## INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer deaths in Europe. In addition, a recent cancer mortality prediction for the year 2013 confirmed that pancreatic cancer is the only cancer which has not had an improvement in European mortality.[1]

Radiation therapy (RT) associated with chemotherapy and surgery has been shown to be an important treatment modality for patients with pancreatic cancer in both adjuvant and neoadjuvant settings.[2-3] However, one of the main limitations of RT is the high radiosensitivity of the surrounding organs at risk, such as duodenal mucosa, small intestine, liver, kidneys, and spinal cord. Because of this, RT is often markedly associated with an increase of severe toxicity especially when a dose escalation to the tumour volume is prescribed.

Intensity-modulated radiation therapy (IMRT) is a recent technique in the delivery of RT. The use

of IMRT is increasingly aimed at generating a more conformal coverage to the tumour volume compared to standard techniques, while maximising the sparing of normal and surrounding critical tissues.

In an aim to investigate the current clinical role of IMRT in the treatment of pancreatic carcinoma, a review of recently published literature was performed.

## RESULTS

Clinical trials between 2001 and 2013 have been selected, analysed, and reported (Table 1, 2, and 3). Only studies investigating clinical outcomes by the use of IMRT for adjuvant and/or locally advanced pancreatic cancer treatment have been included. Studies evaluating only dosimetric parameters have been excluded.

### Conventional Fractionated Radiotherapy

The clinical advantage of conventional fractionated IMRT was shown in some retrospective analysis (Table 1). Compared with conformal RT, IMRT was able to reduce the mean dose to the liver, kidneys, stomach, and small bowel, in 25 patients.[4] 80% of patients experienced Grade ≤2 acute upper gastrointestinal (GI) toxicity. At a median follow-up of 10.2 months, no local failure was noted compared with resected patients. The median survival and distant metastasis-free survival of the 24 patients with adenocarcinoma was 13.4 and 7.3 months respectively. Late liver Grade 4 toxicity occurred in 1/14 patients with a follow-up over 6 months.

Yovino S et al.[5] revised data from 46 patients with pancreatic/ampullary cancer treated with concurrent 5-fluorouracil (FU) and IMRT. Rates of acute GI toxicity for this series of patients were compared with those from RTOG 97-04,[6] treated with three-dimensional conformal techniques. Patients receiving IMRT showed a significant reduction in the incidence of Grade 3-4 nausea and vomiting (0% versus 11%, p=0.024) and diarrhoea (3% versus 18%, p=0.017).

Patterns of first failure were analysed by the same authors in the following study of 71 patients treated with adjuvant IMRT and concurrent chemotherapy.[7] At median follow-up of 24 months, the local failure rate was 69%. Distant metastases, predominantly in the liver, were the most frequent failure pattern (49%). 14 patients (19%) developed locoregional failure. Median overall survival (OS) was 25 months.

Abelson JA et al.[8] reviewed data of 47 patients (29=resected; 18=unresectable) treated by IMRT plus concurrent 5-FU. Four patients (9%) developed Grade ≥3 acute toxicity, and four (9%) developed Grade 3 late toxicity. For adjuvant patients (median survival=1.7 years), the 1 and 2-year OS rate was 79% and 40%, respectively. The 1 and 2-year recurrence-free survival (RFS) rates were 58% and 17%; local-regional control (LRC) rates were 92% and 80%, respectively. For unresectable patients, the 1-year OS, RFS, and LRC rates were 24%, 16%, and 64%, respectively, with a median OS of 7.7 months.

Image-guided radiotherapy (IGRT) offers the possibility of safe margin reduction to generate the planning target volume (PTV) given the reduced interfraction movement through daily imaging. The combination of daily imaging to the steep dose gradient of IMRT may potentially further improve the toxicity of abdominal irradiation. The use of IG-IMRT was investigated in a retrospective analysis of 41 patients, conducted to evaluate the feasibility of ultrasound-based IG-IMRT.[9] Upper GI toxicity Grade ≤2 occurred in 38 patients (92.7%) and lower GI toxicity Grade ≤2 in 39 patients (95.1%). Upper GI Grade 3 toxicity was reported in three patients (7.3%) whereas Grade 4 lower GI toxicity in two patients (4.9%). Mean daily image-guidance corrective shifts were less than 10 mm in all directions, supporting the conclusion that a safety margin reduction and a moderate dose escalation should be afforded by implementation of IG-IMRT.

Trials investigating the role of IMRT with conventional fractionation and concurrent molecular targeted therapy were also conducted (Table 1). In a prospective dose de-escalation trial, patients with resected pancreatic adenocarcinoma received erlotinib and capecitabine concurrently with IMRT.[10] 13 patients were enrolled in two dose levels: erlotinib 150 mg and capecitabine 1600 mg/m$^2$ without interruption (DL 1) and erlotinib 100 mg and capecitabine 1600 mg/m$^2$, Monday to Friday (DL-1). Six of the seven evaluable patients at DL-1 required treatment interruption or dose reduction and four completed planned treatment.

**Table 1. Intensity-Modulated Radiotherapy with conventional fractionation in the treatment of pancreatic carcinoma.**

| | Study design | Pts (n) | Dose RT (Gy) | Dose/ fraction (Gy) | ConcCT | ENI | Acute Toxicities ≥3 (%) | Clinical response (%) | Local Control (%) | Median OS (m) | OS (%) | Late Toxicities ≥3 (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Milano MT, (2004)[4] | Retrospective analysis | 25 R:8; LA :17 | R: 45-50.4 LA: 50.4-59.4 | 1.8 | 5FU | Yes | Leukopenia 16 Anaemia 4 GI 20 | *PR: 50 CR: 10 SD: 30 | LF: 4 (LA) | Overall: 13.4 R: 14.3 LA: 9.3 | Overall: 1y: 55 2y: 22 R, 1y: 83 2y: 50 LA, 1y: 40 2y: 8 | Liver 4 |
| Yovino S, (2011)[5] | Retrospective analysis | 46 R :31; LA:15 | R: 45 LA: 50.4-59.4 | 1.8 | 5FU or Cap | Yes | GI 4 | NS | NS | R: 24.8 LA: 9.7 | NS | GI 4 |
| Yovino S, (2012)[7] | Retrospective analysis | 71 R | 54 -64.8, | 1.8 | Cap or Gem | Yes | GI 8 | NE | LF: 19 | 25 | NS | GI 7 |
| Abelson JA, (2012)[8] | Retrospective analysis | 47 R :29; LA :18 | R: 44-55.8 LA: 39.6-59.4 | 1.8 1.8-2 | Cap or 5FU | Yes | GI 9 | NS | LF: 21 (R) | R: 20.4 LA: 7.7 | R, 1y: 79 2y: 40 LA, 1y: 24 | GI 9 |
| Fuss M, (2007)[9] | Retrospective analysis | 41 R :17; LA :24 | 45-64 | 1.8-2 | Cap or Gem | Yes | GI 12 | NS | NS | 10.3 R: 10.8 LA: 10.0 | 38 | NS |
| Ma WW, (2010)[10] | Dose de-escalation trial | 13 R | 50.4 | 1.8 | Erlotinib + Cap | Yes | Neutropenia 8 GI 38 | NE | NS | NS | NS | GI 8 |
| Pipas JM, (2012)[12] | Phase II | 37 (33 evaluable) R:4; BR: 23; LA: 6 | 45- 54 | 1.8 | Cetuximab + Gem | Yes | Neutropenia 68 Thrombocytopenia 32 Anaemia 3 GI 59 | PR: 30 SD: 61 | LF: 12 (R) | 17.3 R: 24.3 | NS | NS |

Pts: patients; concCT: concomitant chemotherapy; ENI: elective nodal irradiation; R: Resected/resectable; LA: Locally advanced/unresectable; Gem: gemcitabine; 5FU: 5-fluorouracil; Cap: Capecitabine; GI: gastrointestinal; NS: not stated; NE: Not evaluable; PR: partial response; CR: Complete response; SD: stable disease; LP: local progression; LF: local failure; m: months; y: year(s).

Note: GI toxicity includes anorexia, nausea, vomiting, dehydration, diarrhoea, bleeding, small bowel obstruction. *10 LA patients with survival >3 months.

| | Study design | Pts (n) | Dose RT (Gy) | Dose/ fraction (Gy) | ConcCT | ENI | Acute Toxicities≥3 (%) | Clinical response (%) | Local Control (%) | Median OS (m) | OS (%) | Late Toxicities ≥3 (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ben-Josef E, 2012 [13] | Phase I-II | 50 LA | 50- 60 | 2- 2.4 | Gem | No | Neutropenia 56 Thrombocytopenia 13 Anaemia 11 GI 22 | PR: 33 SD: 67 | LP: 17 | 14.8 | 2ys: 30 | NS |
| Vainshtein JM, 2012 [14] | Phase I-II | 38 LA | 50- 60 | 2- 2.4 | Gem | No | NS | NS | LP: 29 | 15.2 | 2ys: 26.6 | NS |

Pts: patients; concCT: concomitant chemotherapy; ENI: elective nodal irradiation; LA: Locally advanced/unresectable; Gem: Gemcitabine; GI: Gastrointestinal; NS: Not stated; Partial response: PR; Stable disease: SD; LP: Local progression; m: months; y: year(s).
Note: GI toxicity includes anorexia, nausea, vomiting, dehydration, diarrhoea, bleeding, small bowel obstruction.

**Table 2. Dose-esclation Intensity-Modulated Radiotherapy in the treatment of pancreatic carcinoma.**

**Table 3. Intensity-Modulated Radiotherapy with altered fractionation in the treatment of pancreatic carcinoma.**

| | Clinical trials | Pts (n) | Dose RT (Gy) | Dose/ fraction (Gy) | ConcCT | ENI | Acute Toxicities≥3 (%) | Clinical response (%) | Local Control (%) | Median OS (m) | 1 y OS % | Late Toxicities ≥3 (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Crane CH, 2001[15] | Phase I | 5 LA | 33 | 3.3 | Gem | Yes | Leukopenia 100 Trombocytopenia 20 Anaemia 20 GI 60 | PR: 20 | LP: 67 | NS | NS | NS |
| Bai YR, 2003[16] | Phase I | 21 LA (16 evaluable) | 3D-CRT: 30+ IMRT: 21-30 | 2 3 | Gem\or 5FU | Yes | Neutropenia 10 Trombocytopenia 5 Anaemia 5 | PR: 31 | NS | NS | 35 | NS |
| Koong AC, 2005[17] | Phase II | 19 LA | IMRT: 45+ SRS: 25 | 1.8 | 5FU or Cap | Yes | GI 11 | SD: 100 | LP: 6 | 7.7 | 15 | 11 |
| Ben-Josef E, 2004[18] | Retrospective analysis | 15 R: 7; LA: 8 | R: 45-54 LA: 54 | 25 1.8-2.16 2.16 | Cap or Celecoxib | Yes | GI 7 | NS | LF: 14 (R) | NS | LA: 69 | NS |
| Ji JS, 2010[19] | Retrospective analysis | 19 LA | 50.4-55 | 1.8-2.2 | Cap | Yes | 0 | PR: 53 SD: 47 | LP: 0 | 6.5 | 36.8 | NS |
| Chang JS, 2012[20] | Retrospective analysis | 39 LA | 45-60 | 1.8-2.2 | Gem or Cisplatin+ Gem or S1 | No | Leukopenia 29 Trombocytopenia 16 Anaemia 10 GI 5 | PR: 53 SD: 39 | LR: 25 | 21.2 | 61.5 | GI 26 |
| Son SH, 2012[21] | Retrospective analysis | 12 LA | 45 or 50 | 3 or 2.5 | 5FU | No | Neutropenia 17 Trombocytopenia 8 | PR: 58 SD: 42 | LF: 8 | 12.1 | NS | NS |

Pts: patients; concCT: concomitant chemotherapy; ENI: elective nodal irradiation; R: Resected/resectable; LA: Locally advanced/unresectable; Cap: Capecitabine; Gem: Gemcitabine; 5FU: 5-Fluorouracil; GI: Gastrointestinal; NS: Not stated; Partial response: PR; Stable disease: SD; LP: Local progression; LF: Local failure; m: months; y: year(s).

Note: GI toxicity includes anorexia, nausea, vomiting, dehydration, diarrhoea, bleeding, small bowel obstruction.

The dose-limiting toxicities were neutropaenia, diarrhoea, and rash. Six patients enrolled in DL-1 completed the planned treatment. Only minor toxicities such as fatigue, elevated liver enzymes, and anorexia were shown with less GI toxicity if compared to conformal RT.[11]

Finally, the efficacy of combination cetuximab plus gemcitabine with IMRT, as neoadjuvant treatment in patients with LAPC, was investigated in a Phase II trial.[12] 37 patients were enrolled, and 33 were assessable for response. 25 patients (76%) underwent resection and 23 (92%) had negative surgical margins. Grade 3 (<10% viable tumour cells) or IV (no viable tumour cells) tumour kill, including two (8%) pathological complete responses (pCR), were found in 24% of resected tumours. Overall, median survival was 17.3 months, compared to 24.3 for resected patients.

## Dose-Escalation Trials

Furthermore, to confirm that dose escalation intensification by IMRT could improve local control and survival, two Phase I/II studies were conducted (Table 2).[13-14] Dose levels were escalated to 60 Gy. In the first study, 50 patients with unresectable pancreatic cancer were accrued.[13] Grade 3-4 GI acute toxicities were observed in 11 patients (22%) and the recommended dose was 55 Gy. Median and 2-year OS were 14.8 months and 30%, respectively. 12 patients (24%) underwent resection (10 R0, 2 R1) with a median survival of 32 months.

38 patients were subsequently analysed by the same authors[14] showing a median survival of 15.2 months and 2-year OS was 26.6% Median progression-free survival (PFS) was 8.6 months. Local and distant progression occurred in 11 patients (29.0%) and 25 patients (65.8%), respectively. The ability of CA19-9 to act as a disease-monitoring biomarker was also demonstrated.

## Altered Fractionated Radiotherapy

The tolerability of IMRT with altered fractionations was also evaluated (Table 3). In one dose escalation trial,[15] hypofractionated (33 Gy/11 fractions) IMRT was delivered in combination with gemcitabine. Five patients were enrolled and treated in two dose levels. All three patients in the first cohort (gemcitabine at 350 mg/m$^2$) suffered from myelosuppression and upper GI toxicity. Therefore, a lower gemcitabine dose (250 mg/m$^2$) was later administered. The acute toxicity profile was confirmed and further investigations were expected.

21 patients with locally advanced pancreatic cancer (LAPC) were enrolled in the following Phase I trial.[16] Patients received doses between 21 Gy to 30 Gy in 7-10 fractions by IMRT following 2 weeks after a conventional RT of 30 Gy/15 fractions. The total escalation tumour dose was 51, 54, 57, 60 Gy, respectively. 16 patients who had completed the RT treatment plan were evaluated. No patient suffered more than Grade 3 acute toxicities.

The efficacy of IMRT in patients with LAPC was confirmed in a Phase II study.[17] 19 patients were enrolled to receive IMRT (45 Gy, 1.8 Gy/day) and concurrent 5-FU followed by a boost with stereotactic radiosurgery (SRS, 25 Gy, single fraction). 16 patients completed the planned therapy. Although Grade 3 toxicity was observed in 2 patients, 15 patients were free from local progression until death with a median OS of 33 weeks.

A low toxicity profile of IMRT was also confirmed in a retrospective analysis of 15 patients.[18] A total dose of 45 or 54 Gy, 1.8 or 2.16 Gy/fraction was delivered in adjuvant or neoadjuvant setting, respectively. Concurrent capecitabine and celecoxib were given to seven patients (73%). Grade 1/2 nausea or vomiting developed in eight patients (53%) and Grade 1/2 haematologic toxicity in nine patients (60%). Only one patient had a gastric ulceration that responded to medical management (Grade 3 GI toxicity). With a median follow-up of 8.5 months, no deaths but one local relapse (14%) were reported in resectable patients. The 1-year survival rate of uresectable patients was 69%.

19 patients with LAPC were enrolled in a study where capecitabine was concurrently administrated with Helical Tomotherapy (HT), an advanced IMRT with integrated CT imaging[19] (total dose=50-55 Gy, 1.8-2.2 Gy/fraction). Overall, in-field response rate was 42.3%. Partial responses were achieved in 53.3% of the pancreatic masses and 25% of regional lymph nodes. With a median follow-up of 6.5 months, no lesion showed in-field progression. Only Grade 1 toxicities were developed.

Data of 39 patients with LAPC treated with RT using high-dose HT (median dose =58.4 Gy) and concomitant chemotherapy were retrospectively reviewed.[20] 29 patients (74%) received gemcitabine during HT. Acute toxicities were acceptable with no GI toxicity higher than Grade 3. Late GI toxicity ≥Grade 3 occurred in 10 patients (26%). The median follow-up was 15.5 months for the entire cohort, and 22.5 months for the surviving patients. Eight patients (21%) were converted to resectable status and a pCR was found in one patient. The 1 and 2-year local PFS rates were 82.1% and 77.3% respectively. The median OS and PFS were 21.2 and 14.0 months, respectively.

Finally, Son et al.[21] evaluated the technical feasibility of hypofractionated HT with concurrent and sequential chemotherapy in 12 patients with LAPC. The total dose delivered was 45 Gy/15 fractions or 50 Gy/20 fractions. Grade 2 acute toxicity was developed in seven patients (58%). No patient showed Grade 3 or worse toxicity. Clinical partial response was reported in 58% of patients and 42% had stable disease. One patient (8%) experienced local progression and 9 patients (75%) experienced distant progression (median follow-up=31.1 months). No patient had regional failure. PFS and OS were 7.6 and 12.1 months, respectively.

## DISCUSSION AND CONCLUSIONS

Pancreatic adenocarcinoma was wrongly considered in the past as a radioresistant tumour. On the contrary, although more data are needed before firm conclusions can be drawn, this tumour can be locally controlled by RT with a total dose of 45-50 Gy as documented by the ability to achieve a complete pathological response rate up to 20%.[18,20,22] Unfortunately, a safe administration of this dose is not easy due to the presence of several radiosensitive surrounding organs; kidneys, liver, small intestine, stomach, duodenum, and spinal cord. Thus, RT for pancreatic cancer currently represents a technological challenge.

In this analysis, we evaluated toxicity and clinical outcomes obtained by the use of IMRT in the last 10 years. As reported, IMRT was able to reduce the irradiation of normal tissue with acceptable grade of acute and late GI toxicity. Unfortunately, most data comes from retrospective analysis or preliminary Phase I or II trials. The only study that compared the toxicity among patients undergoing three dimensional-RT and patients undergoing IMRT, actually compared two different patient populations, one from a randomised and the other from a cohort study.[5] For these reasons the results of this comparison cannot be considered totally credible and generalisable. Moreover, a great heterogeneity regarding recruitment criteria (periampullary, biliary duct and/or pancreatic carcinoma; resectable and/or LAPC), treatment target volumes (elective nodal irradiation or not, different margins for CTV and PTV) and response and toxicity evaluation criteria, was observed.

Based on these considerations, new prospective studies with quality protocols for outcomes evaluation, more standardised contouring guidelines,[23-24] and cost-effective evaluation[25] are needed to better define any clinical benefit of IMRT and to resolve some emerging controversy in healthcare economy related to the technology innovations in radiation oncology and clinical outcomes.

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