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REVIEW ARTICLE

The role of radiotherapy in locally advanced pancreatic cancer

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ABSTRACT

At diagnosis, about 15% of patients with pancreatic cancer present with a resectable tumour, 50% have a metastatic tumour, and 35% a locally advanced tumour, non-metastatic but unresectable due to vascular invasion, or borderline resectable. Despite the technical progress made in the field of radiation therapy and the improvement of the efficacy of chemotherapy, the prognosis of these patients remains very poor. Recently, the role of radiation therapy in the management of pancreatic cancer has been much debated. This review aims to evaluate the role of radiation therapy for patients with locally advanced tumours.

INTRODUCTION

Pancreatic carcinoma is one of the leading causes of cancer-related mortality in the Western world. The International Agency for Research on Cancer estimates that there were 458,918 new cases in 2018 worldwide, and 432,242 patients died of their disease in the GLOBOCAN 2018 study.[1] Pancreatic cancer is projected to be the second leading cause of cancer mortality by 2030.[2] At diagnosis, 15% of patients present with a resectable tumour, 50% with metastatic disease and 35% with a locally advanced tumour.[3] Prognosis of patients with pancreatic cancer is poor with a median overall survival of 16 months in case of locally advanced tumours and 11 months in case of metastatic tumours in recent trials.[4,5] Patients with locally advanced pancreatic cancer (LAPC) have an intermediate prognosis between resectable and metastatic patients. They have tumours that are defined as surgically unresectable without evidence of distant metastases. A tumour is considered to be unresectable if it has superior mesenteric artery (SMA) or coeliac axis encasement of >180 degrees, unreconstructable superior mesenteric vein/portal vein occlusion, aortic involvement or nodal involvement beyond the field of resection.[6] This group needs to be distinguished from patients with borderline resectable (BLR) tumours, where appropriate induction chemotherapy and/or chemoradiotherapy (CRT) may result in secondary resectability. Contrary to BLR tumours, patients with LAPC are very rarely resected and the goal of therapy, like in metastatic disease, is prolongation of survival, symptom palliation and disease control.

The role of radiation therapy (RT) for LAPC has been intensely debated over the past 30 years. Despite advances in chemoradiation and improved systemic agents, patients who present with LAPC experience both high rates of distant metastatic failure and local progression. This review aims to present the evidence based for the use of RT in unresectable LAPC. A search to identify eligible studies was undertaken using the Medline database (from 1980 to 2021). Abstracts of the Proceedings of the Annual Meeting of the American Society of Clinical Oncology, of the American Society of Therapeutic Radiology and Oncology, and of the European Society for Radiotherapy and Oncology were searched ASummary of the trials included in this review is presented in Table 1.

Comparisons between chemotherapy alone and chemoradiation

As early as the late 1960s, external beam RT was used to treat LAPC.[16] Several randomised trials have confirmed the superiority of CRT over RT alone in this indication.[7,8,17] CRT has been compared to chemotherapy in four randomised trials. Three of them were published in the 1980s and only the Gastrointestinal Tumour Study Group (GITSG) trial showed a benefit of CRT with a one-year survival rate of 41

Table 1. Summary of trials included in this review

	Author / year of publication	Treatment	N	Progression free survival (months)	Overall survival (months)	One-year survival (%)
First Studies						
	Moertel et al. 1,969[5]	RT 35–40 Gy	32	6.3 $p < 0.05$	10.4	6[a]
	Moertel et al. 1,981[6]	RT 60 Gy	25	2.9 $p < 0.01$	5.3 $p < 0.01$	10
	Hazel et al. 1,981[7]	5-FU + methylCCNU CRT 46 Gy +5 FU then 5-FU + methylCCNU	30		7.8 n.s. 7.3	
	Klaassen et al. (ECOG) 19,85[8]	5-FU CRT 40 Gy +5 FU then 5-FU	44 47		8.2 n.s. 8.3	32[a] 26[a]
	GITSG 19,88[9]	SMF CRT 54 Gy +5 FU then SMF	21 22		7.4 n.s. 9.7	19 $p < 0.02$ 41
	Chauffert et al. (FFCD-SFRO) 20,08[10]	Gem CRT 60 Gy +5 FU+cisplatine then gem	60 59		13 $p = 0.03$ 8,6	53 32
	Loehrer et al. (ECOG) 20,08[11]	Gem x 7 CRT 50,4 Gy +gem then gem x 5	35 34	6.1 n.s. 6.3	9.2 $p = 0.04$ 11	30[a] 45[a]
	Hammel et al. 20,13[12]	gem ±erlotinib gem ±erlotinib/ CRT 50.4 Gy +cape	136 133	11.8 n.s. 12.5	16.4 n.s. 15.2	
	Krishnan et al. 20,16[13]	Induction FOLFIRINOX/Gem 50–50.4 Gy +gem/cape Induction FOLFIRINOX/Gem 50–50.4 Gy; 57.25 SIB boost +gem/cape	153 47		15 $p = 0.03$ 17.8	57[a] 68[a]
SBRT Studies						
	Schellenberg et al 20,08[14]	C1 gem then 25 Gy single fr. then gem until progression	16		11.4	50
	Herman et al. 20,15[15]	three cycles gem then 33 Gy in five fr. then gem until progression/toxicity	49	7.8	13.9	59
	Park et al. 2017	Group 1: gem/ FOLFIRINOX/ FOLFOX then SBRT 30–33 Gy in five fr. Group 2: gem/ FOLFIRINOX/ FOLFOX then CRT (gem/ cape/ 5-FU) IMRT 45–56 Gy in 25–28 fr.	44 226			56.2 n.s. 59.6

(Continued)

Table 1. (Continued)

	Author / year of publication	Treatment	N	Progression free survival (months)	Overall survival (months)	One-year survival (%)
	Rudra et al 2019	Induction CT, then: MRgRT Low BED : • 40–55 Gy in 25–28 fr. • 30–35 Gy in five fr. MRgRT High BED : • 40–52 Gy in five fr. • 50–67.5 Gy in 10–15 fr.	19 25			45[a] $p = 0.03$ 84[a]
	Chuong et al 2020	91% induction CT, then SMART 50 Gy in five fr. (ENI in 20 patients)	35	7.9	9.8	58.9
	Hassanzadeh et al.	82% induction CT, then SMART 50 Gy in five fr.	44	12.4	15.7	68.2
FOLFIRINOX Studies						
	Pietrasz et al. 2019	FOLFIRINOX then surgery FOLFIRINOX then CRT then surgery (50% of patients)	101 102	13.5 17.7	35.5 57.8	92 93
	Suker et al. 2019	eight cycles FOLFIRINOX then 40 Gy in five fr. (then surgery)	39 (CT and SBRT)		17 From end of SBRT	79 From end of SBRT
	Murphy et al. 2019	eight cycles FOLFIRINOX-Losartan then CRT • resectable:25 Gy in five fr. (cape) • vascular involvement: 50.4 Gy +SIB 58.8 Gy in 28 fr. (cape/ 5-FU)	49 (45 received CRT)	17.5 From start of treatment, $N = 49$	31.4 From start of treatment, $N = 49$	82 a From start of treatment, $N = 49$

N, number of patients; GISTG, Gastrointestinal Study Group; ECOG, Eastern Cooperative Oncology Group ; RT, radiation therapy ; CRT, chemoradiation; 5-FU, 5-fluorouracil; streptozocin, mitomycin-C, and 5-flurouracil; gem, gemcitabine ; cape, capecitabine; SIB, Simultaneous Integrated Boost; SBRT, Stereotactic Body Radiation Therapy; CT, chemotherapy; MRgRT, Magnetic Resonance guided Radiation Therapy; BED, Biological Equivalent Dose; SMART, Stereotactic Magnetic resonance guided Adaptive Radiation Therapy.

versus 19% for chemotherapy alone ($p < 0.02$).[9–11] More recently, in the French FFCD-SFRO Phase III trial, patients with LAPC were randomised between chemotherapy with gemcitabine versus CRT (60 Gy with concurrent cisplatin and 5FU) followed by gemcitabine.[18] The Grades 3–4 toxicity rate was higher with CRT than with chemotherapy alone (66% vs 40 %) with only 42% of patients receiving at least 75% of the planned CRT dose. The median OS was lower with CRT (8.6versus 13 months, $p = 0.03$). At the same time, the American ECOG E4201 randomised Phase III study compared chemotherapy with gemcitabine versus CRT (50.4 Gy with concurrent gemcitabine) followed by gemcitabine.[12] The trial was closed after the inclusion of 74 patients out of the 316 planned due to poor accrual. Median OS was better with CRT than with chemotherapy (11.1*vs* 9.2 months, $p = 0.017$) at the cost of a higher Grade 4 toxicity rate (41 *vs* 9%). However, the small number of patients included reduces the strength of these results.

In a milestone paper, Iacobuzio-Donahue and a team from Johns Hopkins showed on an autopsy series that 30% of patients died with locally destructive pancreatic cancer and 70% with widespread metastatic disease.[13] In this perspective, CRT and chemotherapy are complementary treatments as one has mainly a local effect and the other treats the systemic disease.

Interest of induction chemotherapy

The sequence combining upfront chemotherapy followed by CRT is a therapeutic approach currently widely used. As about 30% of LAPC may have occult metastatic disease at diagnosis, induction chemotherapy can help to select a subgroup of patients without early metastatic progression who could benefit from CRT. This therapeutic strategy has been evaluated in the LAP07 trial. In this international Phase III trial, 442 patients with LAPC were firstly randomised between four months of induction chemotherapy with gemcitabine or gemcitabine and erlotinib. The 269 patients who had no tumour progression after 4 months of chemotherapy underwent a second randomisation between CRT (54 Gy with concurrent capecitabine 800 mg/m^2 bd) and two further cycles of chemotherapy. The median OS was not significantly different between the two arms (15.2 *vs* 16.5 months, respectively; $p = 0.8$).[4] However, patients in the CRT arm had a significantly better local control (68% vs 54%, $p = 0.03$), longer chemotherapy-free

interval before further treatment (6.1 *vs* 3.7 months, $p = 0.02$), and a trend towards improved progression-free survival (HR = 0.78, 95% CI [0.61–1.01], $p = 0.06$). This could translate into a better quality of life. Indeed, except for six patients (5.9%) in the CRT arm who experienced Grade 3 or 4 nausea *versus* none in the chemotherapy group ($p = 0.008$), the adverse toxic effects during the second randomization were not different between the two groups.

These results show that conventionally fractionated CRT can improve local control but has a minimal effect on survival. This could be explained by the high risk of metastatic evolution.[13] Another explanation could be that the RT dose is not high enough to be ablative. This is because RT dose delivery for pancreatic tumours is limited by the radiosensitivity of surrounding organs at risk such as duodenum, jejunum, and stomach. In a retrospective study including 200 patients, Krishnan et al showed that LAPC located at more than 1 cm from luminal organs could receive safely a biologically effective dose (BED) of more than 70 Gy delivered by IMRT with integrated boost technique, inspiration breath hold, and using a daily image guidance.[19] This translated in a benefit in survival (OS of 17.8 months if BED >70 Gy *vs* 15 months if BED ≤70 Gy, $p = 0.03$). The SCALOP-2 study, a Phase II randomised trial, assesses dose escalation. In this trial, patients with LAPC receive induction gemcitabine plus nab-paclitaxel. Those without progressive disease after three cycles are randomised to one of five arms: three more cycles of chemotherapy or CRT with capecitabine with standard- or high-dose RT (50.4 or 60 Gy) with or without concurrent nelfinavir, an AKT inhibitor used as a radiosensitiser.[14] In the USA, the RTOG 1201 Phase II randomised trial had a similar design. Patients with LAPC received first 3 cycles of gemcitabine plus nab-paclitaxel and the patients with no evidence of disease progression were randomised between continuation of chemotherapy until progression or CRT at a standard dose of 50.4 Gy with concurrent capecitabine or intensified IMRT at a dose of 63 Gy with concurrent capecitabine. Unfortunately, this trial was terminated after the inclusion of 20 patients due to poor accrual.

Modern radiation therapy techniques

Until the nineties, patients were treated with conventional external beam RT based on two large parallel-opposed anterior and posterior beams defined by bony landmarks. Thereafter, 3D conformal RT (3DCRT) had been implemented for all patients. More conformal RT techniques, such as intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT), are now commonly used. First, Milano et al reported in 2004 on 25 patients with pancreatic and bile duct carcinomas, comparing IMRT with 3DCRT plans.[20] The dose received by organs at risk (OAR) such as kidneys, liver, and small bowel was significantly reduced with the use of IMRT. In a retrospective series, Yovino et al compared 46 patients treated with IMRT to patients who had 3DCRT in the RTOG 97–04 trial.[15] IMRT significantly reduced the incidence of Grade 3–4 nausea (0% *vs* 11%, $p = 0.024$) and diarrhea (3% *vs* 18%, $p = 0.017$). Ben-Josef et al published the results of a Phase I/II trial of IMRT dose escalation with concurrent gemcitabine in 50 patients with LAPC.[21] Median OS was 14.8 months. The recommended dose was 55 Gy. Interestingly, Krishnan et al have shown in a MDACC cohort that patients who received focal dose escalation with IMRT had an improved OS without additional toxicity.[19]

An emerging approach concerns the use of stereotactic body radiation therapy (SBRT) that could overcome the intrinsic radioresistance of pancreatic adenocarcinomas. Indeed, SBRT permits the precise delivery of a high RT dose per fraction to small tumours, allowing dose escalation while limiting the dose received by adjacent healthy tissues. The reduced duration of radiation therapy also allows effective systemic treatment to not be interrupted for long. The first studies using high doses in 1 to 3 fractions were associated with significant side-effects. In a Phase II study, 16 patients were treated with one cycle of gemcitabine before receiving a single fraction SBRT of 25 Gy (BED 87.5 Gy), then gemcitabine was continued until progression or dose-limiting toxicity.[22] One-year local recurrence-free survival rate was 94%, 6% of patients developed Grade three acute GI toxicity and 47% late toxicity. More recently, a systematic review and pooled analysis reports the results of SBRT with 3 to 5 fractions for a dose of 25 to 40 Gy.[23] In a Phase II trial, 49 patients with LAPC received SBRT (33 Gy in five fractions) with gemcitabine before and after.[24] The tolerance was good with 10 and 6% of acute and late GI toxicity of Grade three or more, respectively. Median OS was 13.9 months and one-year local recurrence-free survival rate was 78%. Four patients (8%) had a secondary R0 resection. These results were disappointing as they were quite similar to those observed with conventionally fractionated CRT. IMRT and SBRT have been compared in a retrospective analysis conducted at Memorial Sloan Kettering Cancer Centre showing similar outcomes with SBRT of 33 Gy in five fractions compared to IMRT of 50.4 to 56 Gy in 28 fractions.[25] The pooled analysis of 19 SBRT studies including 1009 patients with heterogeneous protocols (total dose of 24 to 50 Gy in one to six fractions) showed good tolerance with less than 10% toxicity of Grade three or more.[23] The one-year local recurrence-free survival rate was encouraging (72.5%). The rate of local control seemed to correlate with the total dose and the number of fractions. A recent meta-analysis showed an improved 2 year OS for patients treated with SBRT compared with conventional fractionated radiation therapy (13.7% vs 26.9%) with lower rates of acute Grade 3–4 toxicity (5.6% vs 37.7%).[26] However, the lack of standardization of SBRT protocols, as well as the low level of proof of published studies, mainly retrospective, and the uncertain benefice does not yet allow this therapeutic modality to be recommended outside of a therapeutic trial. In the US, patients with LAPC included in the Phase III trial PANC0015 (NCT01926197) are randomized between chemotherapy with FOLFIRINOX until progression versus the same treatment followed by SBRT. New RT techniques such as stereotactic MR-guided online adaptive radiation therapy (SMART) made possible by the development of the MR-linear accelerator allow RT dose escalation. With the MR-linear accelerator, it is possible to visualize the tumour continuously intrafraction and to create a daily plan that optimizes dose to the tumour and conforms it to the organs at risk. In a retrospective study, Rudra et al found patients receiving a BED >70 Gy, by using SMART or MR guided conventionally fractionated or hypofractionated RT, had a higher

2 year OS rate.[27] However, patients in the high-dose group had significantly smaller tumours. In another retrospective study conducted by a team from Miami, 35 patients were treated with SMART at a dose of 50 Gy in five fractions (BED 100 Gy).[28] Eighty percent had LAPC and most received induction chemotherapy. With a median follow up of 10.3 months, the rate of acute and late toxicity was low (2.9 and 2.9%, respectively). In terms of efficacy, the results were quite disappointing with a one-year local control rate of 87.8% and one year OS of 58.9%, similar to those reported by Herman et al with a SBRT dose of 33 Gy in five fractions.[24] Likewise, St. Louis, Missouri, reported the outcomes of 44 patients treated with SMART at a dose of 50 Gy in five fractions with daily adaptation.[29] The tolerance was very good with no acute Grade 3–4 toxicity and 4.6% Grade three late toxicity. Although all patients were considered to have LAPC at initial diagnosis, four patients were deemed resectable after SMART with one pathologic complete response and one near pathologic complete response with 5% residual viable tumour and a negative margin resection; and with three alive at last follow-up. One-year local control was 84%. However, median OS was 15.7 months, similar to that observed in the CRT arm of LAP07 trial.[4] In a Phase I trial, 20 patients with abdominal tumours were treated with SMART at a dose of 50 Gy in five fractions with daily adaptive plans to preserve OAR constraints and dose escalation.[30] Among them, five had pancreatic cancers. Online adaptive plans were created for 81/97 fractions. None Grade three acute toxicity was observed. A prospective single-arm Phase II multicentric study (NCT03621644) assessing SMART 50 Gy in five fractions for LAPC is ongoing.

What role for radiation therapy in the era of modern chemotherapy regimens?

More recently, the improved effectiveness of new chemotherapy combinations opens up new hopes. Phase III trials comparing gemcitabine to FOLFIRINOX (PRODIGE 4/ACCORD 11) or to a combination of gemcitabine and nab-paclitaxel (MPACT) demonstrated the superiority of these regimens over gemcitabine in metastatic patients.[31,32] Likewise, in a Phase II study evaluating the combination of gemcitabine and nab-paclitaxel for patients with LAPC, the median duration of tumour control was 9 months and the response rate was 34% with a median OS of 18.8 months.[33] Of note, only 17% received CRT in this trial. Chemotherapy with FOLFIRINOX is currently compared to gemcitabine in patients with LAPC in NEOPAN randomised trial (NCT02539537).[34] In NEOLAP Phase II randomised trial, patients with LAPC receiving an induction chemotherapy with FOLFIRINOX had a non-significant higher rate of secondary resection (45% in the FOLFIRINOX group versus 30.6% in the gemcitabine-nab-paclitaxel group (p = 0.135) and improved median OS (22.5 months in the FOLFIRINOX group versus 17.2 months in the gemcitabine-nab-paclitaxel group (p = 0.268).[34]

Several teams have reported their experience of using FOLFIRINOX for patients with BLR or LAPC in retrospective series. In the meta-analysis published by Suker et al in 2016, 13 studies including 689 patients (52% of them with LAPC) treated with FOLFIRINOX were analysed.[35] For patients with LAPC treated with FOLFIRINOX, the resection rate was 26% with R0 resection margins in 78% of cases. This translated into an encouraging median overall survival of 24.2 months, considering all included patients. It should be underlined that 63.5% of the patients also received CRT. Retrospective studies such as Pietrasz et al show an increased rate of R0 resection in patients who received CRT after induction FOLFIRINOX.[36] In this retrospective study, 203 patients with BLR (n = 106) or LAPC (n = 97) resected after induction FOLFIRINOX with (50%) or without (50%) CRT were included. Patients who received CRT had higher R0 resection rate (89.2% vs 76.3%; p = 0.017), ypN0 rate (76.2% vs 48.5%; p < 0.001), pathologic major response rate (33.3% vs 12.9 %; p = 0.001), lower rate of locoregional relapse (28.3% vs 50.7 %; p = 0.004), and longer median OS (57.8versus 35.5 months; p = 0.007) than those receiving FOLFIRINOX alone. However, a major bias of analysis was that patients were included based on secondary resection. The delay between diagnosis and secondary resection was three months longer in case of CRT. Thus, the better results reported after CRT could be explained by a selection effect of CRT (patients who progressed shortly after CRT were not operated) and/or an additional efficacy of CRT on pancreatic tumour. The LAPC-1 Phase II trial included 50 patients with LAPC. They were treated with eight cycles of FOLFIRINOX followed by SBRT at a dose of 40 Gy in five fractions.[37] Only 62% of patients received the eight planned cycles of FOLFIRINOX and 78% the SBRT. SBRT was well tolerated with only 5% of Grade 3–4 acute toxicity, although there were two deaths due to gastro intestinal bleeding after SBRT. One-year OS was 64%. Six patients (12%) had a secondary tumour resection with two pathological complete responses. In a recently published single-arm Phase II trial, 49 LAPC patients received FOLFIRINOX and losartan, an angiotensin II receptor antagonist, for eight cycles.[38] Then, patients with resectable tumour (16%) received short-course protontherapy (5 GyE ×5) with capecitabine while the others (84%) received long-course CRT (50.4 Gy with a vascular boost to 58.8 Gy) with capecitabine. Thirty-four patients (69%) had subsequent tumour resection with 88% of R0 margins. Median OS was 31.4 months for the whole population and 33 months for resected patients. Even if the number of included patients was quite low, these results are very promising with a higher rate of resection than expected in this population and longer survival. Overall, a strategy combining an induction chemotherapy followed by CRT, otherwise called total neoadjuvant treatment, could optimize the chances of making LAPC resectable. Indeed, the outcome of these patients is improved when a surgical resection is feasible. In the NEOLAP Phase II randomised trial, secondary resection was associated with improved overall survival (27.4 *vs* 14.2 months; p = 0.0035).[34]

CONCLUSIONS

The prognosis for pancreatic adenocarcinoma remains poor, but glimmers of hope have recently appeared. For LAPC, the first-line treatment is chemotherapy because of the high risk of metastatic evolution. An intensified regimen such as FOLFIRINOX or gemcitabine plus nab-paclitaxel could improve outcomes. RT should be discussed for patients with controlled disease after at least 4 months of chemotherapy. The optimal technique of RT is under evaluation. Indeed, improvements in RT techniques, especially SBRT and SMART, could improve the results, although

evidence of their superiority compared to conventional CRT is currently lacking.

COMPETING INTERESTS

FH has received personal fees from Merck Serono, BMS, MSD, Astra Zeneca, Shire, and Servier. JBB has received personal fees from Amgen, AstraZeneca, Bayer, Merck Serono, Pierre Fabre, Roche, Sanofi, Servier, Shire, and non-financial support from Amgen, Merck Serono, and Roche.

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