

# Which patients with locally advanced pancreatic cancer treated with induction chemotherapy are most likely to benefit from post-induction chemoradiotherapy?

Sophie Otter, Irene Chong, Ria Kalaitzaki, Diana Tait

## ABSTRACT

**Aims:** The role of concomitant chemotherapy with radiotherapy (CRT) in locally advanced pancreatic cancer (LAPC) is controversial. The aim of this study was to report the outcomes of patients with LAPC treated with CRT over a 10-year period within a single institution and to identify those patients who derived the most benefit. **Methods:** Patients with LAPC who received radical radiotherapy ( $\geq 45\text{Gy}$ ) between January 2004 – October 2014 were identified. The Electronic Patient Record was reviewed to collect data regarding staging, treatment, response and outcome. The Kaplan-Meier and Cox regression methods were used to analyse survival outcomes and compare survival rates between groups. **Results:** 138 patients were identified. Patients who had a response on imaging after induction chemotherapy had a median OS of 17.4 months compared to 10.3 months in non-responders (HR 0.55, 95% CI 0.35–0.87,  $p=0.01$ ). At three months post-radiotherapy, patients who had achieved a response on CT had a median OS of 56 months compared to 10.7 months (HR 0.28, 95% CI 0.12–0.65,  $p=0.003$ ). However, a reduction in CA19-9 prior to radiotherapy was not significantly associated with progression free survival (PFS)

or Overall survival (OS). Patients with a response in CA19-9 levels at 3-months post-radiotherapy compared to baseline had an OS of 19.1 months compared to 10.5 months in non-responders (HR 0.42, 95% CI 0.26–0.68,  $p<0.001$ ). **Conclusion:** Patients with LAPC who responded to chemotherapy on imaging prior to radiotherapy had improved PFS and OS than non-responders and therefore appeared to benefit the most from CRT. A decrease in CA19-9 prior to radiotherapy was not associated with improved survival and proved less useful for patient selection for CRT.

**Keywords:** Chemoradiotherapy, Pancreatic cancer, PET-CT

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## INTRODUCTION

Pancreatic cancer is the tenth most common cancer in the UK. In 2013, there were 9,408 new cases of pancreatic cancer. The 10-year survival in England and Wales from 2010–2011 was <1% [1]. Patients with locally advanced disease have an overall survival of 6–11 months [2].

In 1981, the Gastrointestinal Tumor Study Group showed that radiotherapy with bolus 5FU was superior to radiotherapy alone with a one year survival of 40% v. 10% [3]. However, there is still some controversy about the role of CRT (concomitant chemotherapy with radiotherapy) versus chemotherapy alone in the treatment of locally advanced pancreatic cancer (LAPC), largely due to differences in chemotherapy regimens, scheduling and duration.

A phase three randomised controlled trial (LAP07) compared chemotherapy alone (gemcitabine +/- erlotinib) for six months with induction chemotherapy (gemcitabine +/- erlotinib) for four months followed by chemoradiotherapy (54Gy in 30# with capecitabine) [4]. There was no significant difference in overall survival (OS) between the chemotherapy and the chemoradiotherapy arms. The rate of local recurrence was lower in patients receiving chemoradiotherapy 32% vs 46%,  $p=0.03$ ) and there was no increase in grade 3 or 4 toxicities. However, it should be noted that the induction chemotherapy was only for four months and that patients received gemcitabine alone rather than a doublet or triplet chemotherapy regimen.

A meta-analysis in 2007 identified two randomised controlled trials which compared CRT followed by chemotherapy with chemotherapy alone where no improvement in OS in the CRT arm was observed (two trials, 134 patients, HR 0.79; 95% CI 0.32–1.95) [5]. A study undertaken by Chauffert et al. revealed a survival disadvantage for CRT compared to chemotherapy but incorporated a regimen of cisplatin and 5FU in combination with radiotherapy that was poorly tolerated and which would not be considered standard treatment [6].

However, there are other studies which suggest a positive role for radiotherapy in patients with LAPC [7, 8]. A phase two randomised trial of patients with LAPC ( $n=74$ ) compared six cycles of gemcitabine with chemoradiotherapy (weekly gemcitabine, 50.4 Gy in 28#). There were more grade four and five toxicities (41% v 9%) in the CRT arm but grade 3 and 4 toxicities were similar. Survival in the chemotherapy arm was 9.2 months compared to 11.1 months in the chemoradiotherapy arm ( $p=0.017$ ) [7].

Furthermore, three retrospective studies have reported an improvement in OS. Choi et al. reported that patients with unresectable LAPC who received concurrent CRT had a significantly improved OS of 15.4 months compared to 9.3 months in patients who had chemotherapy alone ( $p=0.011$ ). HR for OS was 0.536 ( $p=0.003$ ) [9]. Huang et al. also retrospectively identified a survival benefit for chemoradiotherapy over chemotherapy alone (OS 14.6 months v 8.1 months,  $p=0.001$ ) [10].

The SCALOP trial was a phase 2 trial randomising patients to chemoradiotherapy with either gemcitabine or capecitabine after 16 weeks of induction gemcitabine and capecitabine chemotherapy. There was no control

arm of continuing with chemotherapy alone but the results showed that the capecitabine regimen had an improvement in median OS of three months (although the HR was not significant) and was less toxic than the gemcitabine arm [11, 12]. SCALOP2 is currently recruiting and is investigating both dose escalation of radiotherapy to 60Gy in 30# and also the addition of nelfinavir (a protease inhibitor which inhibits the Akt/PKB pathway) to chemoradiotherapy [13]. The trial design includes a chemotherapy only arm and also an observation arm. The combination of novel drugs with radiotherapy and dose escalation will hopefully lead to further improved local control and overall survival.

From the available literature, with conflicting results and an inability to demonstrate an overall role for CRT in LAPC, the benefit of CRT may be in a select group of patients and therefore selection criteria for CRT need to be better defined. We report the outcome data of 138 consecutive patients receiving CRT at a single institution. In addition, we focus on the utility of imaging response assessments after neo-adjuvant chemotherapy and changes in CA19-9 levels in an attempt to identify patients who had improved survival following chemoradiotherapy.

## MATERIALS AND METHODS

Patients with LAPC who, after induction chemotherapy, were treated with radiotherapy at a dose of 45Gy or greater at a single institution between January 2004 – October 2014 were identified. Their Electronic Patient Record was reviewed to collect data regarding demographics, staging investigations, radiotherapy and chemotherapy details, response to treatment and outcome. Responders on imaging (PET-CT or CT) were defined as those patients who had either complete response (CR) or partial response (PR) using Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Overall survival (OS) was defined as the time from radiotherapy start date to death from any cause whilst progression free survival (PFS) was measured from radiotherapy start date to date of progression or death from any cause. The start of radiotherapy was chosen as it was a more definitive time point particularly as some patients had been diagnosed at other institutions and may have received their induction chemotherapy elsewhere making the date of diagnosis more difficult to define. Patients without an event were censored at last follow up. The Kaplan-Meier method was used to summarise the survival estimates whilst Cox regression method was used to compare the survival rates between groups. CT imaging and CA 19-9 were routinely performed for staging and response assessment. PET was not used routinely for staging before 2008 and has not been a routine part of response assessment at our institution.

## RESULTS

### Patient demographics and tumour staging

Between January 2004 – October 2014, 138 patients with pancreatic cancer were treated with radical radiotherapy (doses >45 Gy). Baseline characteristics are displayed in Table 1. Although there was no formal TNM staging documented on radiology reports for staging investigations or in the MDT (multidisciplinary team) summary for 51.5% (71/138) patients, the majority of these cases were documented as locally advanced disease by specialist radiologists who defined this as encasement of vessels or other local spread contraindicating surgery. The PFS for the whole cohort was six months (IQR 3.7-10.3 months) and OS was 12 months (IQR 6.6-22.7 months).

### Treatment details

97.1% (134/138) of patients received chemotherapy prior to radiotherapy (Table 2). Although the four patients who did not receive induction chemotherapy had ECOG performance statuses of 1-2, they were aged 72-86 and therefore may have had other comorbidities that precluded the delivery of systemic treatment. The majority of patients (80/134, 59.7%) received between 4-6 months of chemotherapy. A minority (6/134, 4.4%) switched from one chemotherapy regimen to another due to progression or toxicity.

84.8% (117/138) of patients received concurrent CRT (Table 2). Of the patients receiving concurrent CRT, 87.2% (102/117) completed the full course of concurrent chemotherapy. 7.2% of patients (10/138) had their radiotherapy terminated early. 91.3% (126/138) of patients tolerated radiotherapy with or without chemotherapy well and without any grade 3 or 4 toxicities.

### PET scans

67% of patients had a PET-CT scan at presentation. This was in addition to a staging CT scan which was performed on all patients. The majority of patients who were not staged with a PET-CT scan were treated prior to 2008 when PET-CT was less readily available. Following induction chemotherapy, 21 patients (15.7%) had a further PET-CT scan. In 10 of those patients the PET-CT and CT results were consistent, 8 patients had a greater response on PET-CT (for example complete metabolic response on PET-CT compared to PR on CT), 1 patient had PR on CT but stable disease on PET-CT and 2 patients did not have a corresponding CT result that was available. At relapse, 32/122 (26.2%) had PET-CT scans.

### Response on imaging and Survival Outcomes

The schema for the treatment and imaging schedule followed is outlined at the top of Table 3. CT response to induction chemotherapy is shown, as is the CT response

at 3 months post-completion of chemoradiation. Of the 33 patients that progressed at the 3 month post radiotherapy imaging point, 19 (57.6%) had distant metastases, 8 (24.2%) had local progression only and 6 (18.2%) had both local and distant progression.

Those that responded on imaging criteria (CR or PR on PET-CT or CT) after induction chemotherapy had a median PFS of 7.5 months compared with 5.3 months for those assessed as non-responders (Figure 1 (A), HR 0.72, 95% CI 0.48-1.07,  $p=0.11$ ). Responders had a median OS of 17.4 months whilst non-responders had a median OS of 10.3 months (Figure 1 (B), HR 0.55, 95% CI 0.35-0.87,  $p=0.01$ ).

Of the 19 patients who relapsed, 16 went on to receive second line chemotherapy or radiofrequency ablation (Gemcitabine / capecitabine =9, Folfox=3, Gemcitabine / abraxane=1, Folfox=1, Gemcitabine / oxaliplatin =1 and RFA=1).

The PFS and OS results for the patient groups classified as responders and non-responders at 3 months post completion of chemo-RT are shown in (Figure 2A and B).

### CA19-9 Response and survival outcomes

89 (71.8%) patients had a decrease in CA19-9 from baseline to pre-CRT and 35 (28.2%) had no change or an increase (the remaining patients had blood tests results missing as they were performed at other hospitals). 25 patients had a decrease in CA19-9 from pre-CRT to 3 months post-CRT time points and 75 had either no change or an increase.

Neither PFS nor OS was significantly correlated with a fall in CA19-9 after induction chemotherapy and before the start of CRT. Comparing CA19-9 responders with non-responders, PFS was 6.7 months compared with 4.1 months and median OS 13 months compared with 9.6 months. However, there was a significant improvement in PFS in patients showing a decrease in CA19-9 from baseline to 1 month post-radiotherapy, 7.5 months compared to 3.6 months, HR 0.43 (95% CI 0.27-0.69,  $p<0.001$ ). Similarly with OS, those with any decrease had a median OS of 14.4 months compared to 7.3 months in those without, HR 0.58 (95% CI 0.35-0.95,  $p=0.03$ ). This effect persisted at the 3 months post radiotherapy assessment with a PFS of 9 months compared to 5.3 months, HR 0.43 (95% CI 0.27-0.69  $p<0.001$ ) and OS 19.1 months compared to 10.5 months, HR 0.42 (95% CI 0.26-0.68),  $p<0.001$ ).

CA19-9 level pre-radiotherapy compared with those at 3 months post radiotherapy showed a similar effect. Median PFS was 11.7 months in those with any decrease and 5.7 months in those without, HR 0.37 (95% CI 0.22-0.63,  $p<0.001$ ). The median OS figure for the two groups was non-significant with figures of 20.6 months compared with 11.0 months, HR 0.44 (95% CI 0.25-0.77,  $p=0.01$ ).

Table 1: Baseline patient and treatment characteristics

Characteristics	Category	Frequency, n=138 (%)
Gender (%)	Male	75 (54%)
	Female	63 (46%)
Age (%)	40-49	8 (5.8%)
	50-59	33 (23.9%)
	60-69	58 (42.0%)
	70-79	35 (25.4%)
	80-89	4 (2.9%)
Performance status (%)	0	32 (23.2%)
	1	58 (42.0%)
	2	10 (7.2%)
	3	1 (0.7%)
	Not documented	37 (26.8%)
T staging (%)	T2	5 (3.6%)
	T3	13 (9.4%)
	T4	46 (33.3%)
N staging (%)	No	33 (23.9%)
	N1	29 (21%)
	N2	2 (1.4%)
Locally advanced	No formal TNM staging	71 (51.5%)
Metastatic (%)	M1	3 (2.2%)
CA 19-9 at presentation	190.5 (median)	41 – 905 (range)
PET at presentation	Yes	92 (66.7%)
	No	46 (33.3%)
Radiotherapy dose	45Gy in 25#	2 (1.4%)
	50.4Gy in 28#	44 (31.9%)
	54Gy in 30#	89 (64.5%)
	60Gy in 30#	3 (2.2%)

Table 2: Induction and concurrent chemotherapy rates

Type of chemotherapy	Chemotherapy received?	Frequency (%)	Regimen	Frequency
Induction chemotherapy	Yes	134 (97.1%)	Gemcitabine Gemcitabine / capecitabine Trial FOLFIRINOX Other	14 (10.4%) 63 (47%) 33 (24.6%) 17 (12.7%) 7 (5.2%)
	No	4 (2.9%)		
Concurrent chemotherapy	Yes	117 (84.8%)	Capecitabine Other	110 (94%) 7 (6%)
	No	21 (15.2%)		



**Surgery**

16 of the 138 patients in this series (11.6%) proceeded to radical surgery following completion of chemoradiation. eight received Folfirinox as induction chemotherapy, six received gemcitabine / capecitabine and the remaining patients received gemcitabine / oxaliplatin or trial regimens.

The PFS for patients who proceeded to surgery (16/138, 11.6%) was 20.3 months compared to 5.3 months for those who did not (HR 0.21, 95% CI 0.10 to 0.43, p<0.001) whilst OS was 43.5 months and 10.7 months respectively (HR 0.21, 95% CI 0.09 to 0.49, p<0.001 (Figure 2 (C) and (D)).

**Patterns of recurrence following CRT**

Relapse, at any time point, was with distant metastases in 48.6% (67/138) of patients, local recurrence in 23.9% (33/138) and both distant and local disease in 8% (11/138). No relapse was documented for 19/138 patients (13.8%). The remaining 5.8% (8/138) were lost to follow up, were presumed to have metastases but were never imaged or had metastases found at surgery. Sites of relapse in order of frequency were pancreas 22.5% (31/138), liver 19.6% (27/138) and peritoneum 17.4% (24/138). Of those with documented relapse, 53.8% (64/119) went on to have further treatment with either chemotherapy, radiofrequency ablation or palliative radiotherapy.

**DISCUSSION**

The incidence of pancreatic cancer is predicted to increase due to an increase in risk factors such as obesity and diabetes. This, coupled with the poor prognosis, means that it is a significant cause of morbidity and mortality worldwide. However, intriguingly there are some patients who do well and therefore this is a

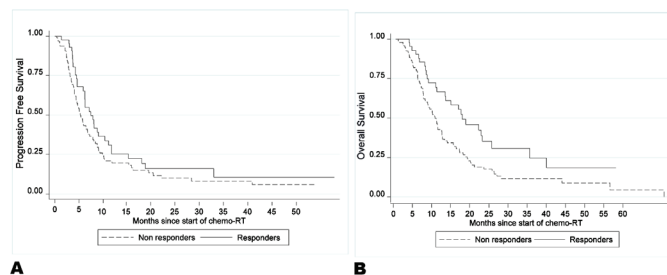


Figure 1: PFS (A) and OS (B) for responders and non-responders to induction chemotherapy assessed on imaging. PFS and OS are measured from the start of radiotherapy. Doublet / triplet chemotherapy included gemcitabine / capecitabine, FOLFIRNOX and trial regimens.

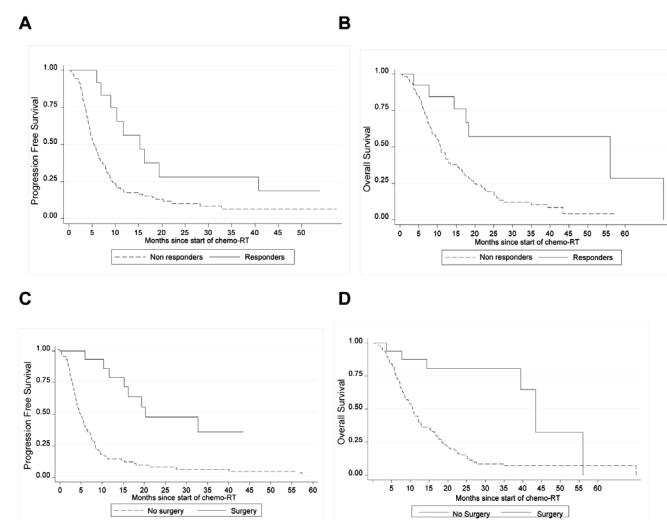


Figure 2: PFS (A) and OS (B) according to imaging response three months post chemoradiotherapy. PFS (C) and OS (D) according to whether patients proceeded to surgery.

Table 3: Schema of treatment and imaging scheduling showing response to induction chemotherapy (compared to CT at diagnosis) and response to chemoradiotherapy (compared to CT pre-radiotherapy).

Baseline staging and imaging	Induction chemotherapy	Response to induction chemotherapy assessed by CT	(Chemo)-RT	CT Response 3 month post-(Chemo)-RT
CT response	n=134		n=138	
Complete Response		0 (0%)		3 (2.1%)
Partial Response		38 (28.4%)		10 (7.3%)
Stable Disease		76 (56.7%)		68 (49.3%)
Progressive Disease		14 (10.4%)		33 (23.9%)
Results not available/ applicable		6 (4.5%)		24 (17.4%)

heterogeneous disease presenting challenges in selection for treatment approaches.

The role of chemoradiotherapy remains controversial in the management of locally advanced pancreatic cancer but there is a subset of patients who appear to benefit and the aim of this retrospective study was to try to identify those patients. These patients may have an improved prognosis due to the molecular profile of their disease that could confer a more indolent phenotype facilitating the successful delivery of localised treatment. In this series, the patients that had particularly good outcomes after chemoradiotherapy were the 13 patients that showed an imaging response 3-month post-radiotherapy (median OS 56 months). 8 of these 13 went on to have a Whipple's procedure. Therefore, the role of CRT may be particularly important in downstaging a small group of LAPC patients thereby allowing them to proceed to surgery. However, the next conundrum is how to identify these patients upfront that are initially felt to be locally advanced but over the course of chemotherapy and CRT become operable.

It may be that surgery should be the ultimate goal of using chemoradiotherapy in LAPC as other studies have also demonstrated better survival in patients able to undergo surgery following chemoradiation. A multicentre UK retrospective study reported improved survival (27 m v 6m,  $p=0.023$ ) in patients undergoing resection [14]. However, surgery is not an option for the majority of patients as was seen in a further retrospective series in which only 1 of 54 patients proceeded to resection [15]. This latter study was small but there is a large systematic review of 111 studies which has shown that approximately one third of patients deemed to have unresectable disease at diagnosis, became resectable after neoadjuvant treatment and had comparable survival to those patients who had been deemed to be resectable upfront [16].

The rationale for intensifying local treatment, such as surgery or radiotherapy is supported in our study with 24% of relapsing patients having local disease only. As far as radiotherapy is concerned, there are a number of approaches that might be used to reduce local recurrence rates and dose escalation is now a reality using more advanced radiotherapy techniques. For example, patients treated with higher doses (BED >70 Gy) achieved with intensity modulated radiotherapy (IMRT) and simultaneous integrated boost, have a superior OS (17.8 vs 15.0 months,  $p=0.03$ ) [17]. IMRT together with image guided radiotherapy (IGRT) may allow greater certainty in terms of tumour localization and accuracy of delivery, and therefore permit a safe reduction in radiotherapy planning margins [18].

The precision of tumor delineation also needs to be taken into consideration as there is considerable variability of tumour outlining between oncologists even in trials such as the SCALOP trial where there was a clearly defined protocol [19]. Other imaging modalities such as PET-CT may allow more accurate target delineation and therefore improve local control [20]. Pre-

chemoradiotherapy PET-CT parameters (SUVmax <6.2) has also been shown to predict patients that are less likely to metastasise and therefore may benefit most from local treatment intensification [21].

Treatment delivery may also be further improved with the introduction of the MR linear accelerator. This, combined with diagnostic and planning MRs, may increase target volume and treatment delivery certainty. Other approaches that allow radiotherapy dose escalation include Stereotactic body radiotherapy (SBRT) [18, 19]. SBRT in 3–5 fractions either preceding or following systemic chemotherapy has been shown in non-randomised studies to improve local control rates with an acceptable toxicity profile [22, 23].

Although there was a significant local only relapse rate (24%) in our series, as expected, the majority of patients relapsed with systemic disease. This emphasises the importance of considering this disease as a systemic problem and the need to also look at ways of improving systemic therapy. For example, there may be a role for maintenance chemotherapy. This approach has already shown promise in patients who have had their pancreatic cancer resected and who had an improved survival, compared with adjuvant chemotherapy alone, by the introduction of maintenance chemotherapy [22]. As yet, there are no phase III trials to provide definitive evidence for this approach and, similarly, other strategies to reduce distant metastases might involve novel drugs in combination with conventional chemotherapy.

Overall, our results confirm that imaging response after induction chemotherapy and post chemoradiation, predicts for improved PFS and OS. High resolution imaging, including MRI, may provide an even finer handle on the impact of treatment on tumour structure and function. However, the presented results on the role of CA19-9 don't support the use of marker-response as a reliable means of identifying good outcomes, at least after induction chemotherapy. The better outcomes for patients demonstrating a fall in CA19-9 after chemoradiation doesn't help in selecting patients for Chemoradiotherapy but may help in discussions on prognosis after treatment.

Although this study has limitations including its retrospective nature and limited size, it represents a valuable resource describing our experience in treating patients with locally advanced pancreatic cancer over the last decade. There has been a consistent approach of aiming to deliver 6 months of neoadjuvant chemotherapy prior to chemoradiation and the present population provides a significant sample size for this strategy. Furthermore, the reported population is representative of the LAPC cancer population as a whole, rather than just those selected for trial inclusion. However, in order to fully determine the contribution of chemoradiotherapy to the outcome of these patients, a control arm of patients who received no chemoradiotherapy would be needed. This would therefore determine whether the patients who responded well to induction chemotherapy would have

continued to have an improved survival with or without CRT.

## CONCLUSION

In this study, we observed that patients who responded to induction chemotherapy on imaging, prior to radiotherapy, achieved an improved PFS and OS compared with non-responders and appeared to derive the greatest benefit from CRT. It seems reasonable, therefore, to suggest that radiological response following induction chemotherapy could be useful in the selection of patients for subsequent CRT. Although we cannot definitively conclude that the addition of CRT contributed to these improved outcomes, it would be worthwhile to prospectively evaluate the utility of imaging response following induction chemotherapy as a radiological biomarker to stratify patients for subsequent local therapy.

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**Author Contributions**

Sophie Otter – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

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Authors declare no conflict of interest.

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