Abstract

Aims: To determine the efficacy of induction gemcitabine followed by biweekly gemcitabine concurrent with radiotherapy for locally advanced pancreatic cancer.

Materials and methods: Between March 2001 and August 2009, 90 patients with unresectable (78) or resected (12) pancreatic cancer were treated with a standard treatment policy of induction gemcitabine (seven doses of weekly gemcitabine at 1000 mg/m²) followed by concurrent radiotherapy (52.5 Gy) and biweekly gemcitabine (40 mg/m²).

Results: After induction gemcitabine, 17.8% of patients did not proceed to chemoradiotherapy, due to either disease progression, performance status deterioration or gemcitabine toxicity. Of the patients who received chemoradiotherapy, 68.9% completed the course of 52.5 Gy, whereas 79.7% received more than 45 Gy. Chemoradiotherapy was stopped early due to treatment toxicity in 22.9% of patients. On intention to treat analysis, the median overall survival was 12.7 months in the locally advanced group and 18.2 months in the resected group. On multivariate analysis for the unresectable patients, a larger gross tumour volume was a significant poor prognostic factor for overall survival and local progression-free survival.

Conclusion: This large series confirms, in a standard practice setting, similar efficacy and tolerability of treatment as previously reported in our phase I–II study. The benefit to patients with a gross tumour volume >48 cm³ may be limited.

Key words: Chemoradiotherapy; induction gemcitabine; pancreatic cancer

Introduction

Pancreatic cancer is the 12th most commonly diagnosed malignancy, yet it is the fourth leading cause of cancer mortality in the Western world [1]. Surgery is the only potentially curative treatment. However, only 10–20% of patients present with resectable disease and even within this favourable group, the 5 year overall survival is only 20% [2]. A further 29% of patients present with unresectable locally advanced pancreatic cancer (LAPC) that is not considered curable with current treatment techniques [3]. There remains a lack of worldwide consensus on both the most appropriate adjuvant treatment for patients with resectable disease [4–6] and the most effective definitive treatment for patients who have unresectable LAPC [7–9].

Brade et al. [10] established the safety and efficacy of seven doses of weekly induction gemcitabine followed by
biweekly gemcitabine concurrent with radiotherapy to
52.5 Gy in 30 fractions for the treatment of unresectable
LAPC \((n = 21)\) and for resected pancreatic cancer \((n = 14)\).
The median survival was 13.9 and 18.4 months, respectively.
The radiosensitising effects of gemcitabine are short lived,
hence the biweekly administration \([11]\). There are currently
no phase III data to support the use of induction chemo-
therapy before chemoradiotherapy. However, phase II
studies and retrospective series \([12–15]\) have suggested a
benefit to this approach and this strategy can select out
patients who are destined to develop early metastatic dis-
ease. After the completion of the phase II study investi-
gating induction gemcitabine followed by chemoradiotherapy
\([10]\), this strategy became the standard
treatment protocol at our hospital for unresectable disease
and postoperatively for positive or close margins. The
objective of the present retrospective series was to deter-
mine the efficacy of this strategy in a larger series and
outside the setting of a phase II protocol.

**Materials and Methods**

**Patients**

The radiotherapy and chemotherapy databases at the
Princess Margaret Cancer Centre, in addition to the Ontario
Cancer Registry, were used to identify patients treated from
March 2001 to August 2009 at the Princess Margaret Cancer
Centre, Toronto, Ontario, Canada. Patients eligible had
either resected or unresectable, non-metastatic pancreatic
cancer treated with induction gemcitabine and concurrent
chemoradiotherapy. Patients were included on an intention
to treat basis and the chemotherapy database was used to
ensure all patients who were started on weekly gemcitabine
with the intention to proceed to chemoradiotherapy, but
did not due to disease progression or treatment toxicity,
were captured.

Patients were excluded if they were enrolled on our
previous phase I–II trial \([10]\). All patients had a pathological
diagnosis of adenocarcinoma of the pancreas, except for
three patients who had a clinical diagnosis. Peri-ampullary
tumours were not included in this study.

**Treatment**

Patients received induction weekly gemcitabine chemo-
therapy, 1000 mg/m\(^2\), for 7 weeks. A repeat computed to-
mography scan of chest, abdomen and pelvis was carried
out between weeks 5 and 7. In the event of no progression
(local or distant), the patient proceeded to chemo-
radiotherapy after a 1 week break. The concurrent chemo-
therapy consisted of gemcitabine biweekly at 40 mg/m\(^2\)
for the entire duration of radiation. The prescribed dose of
radiotherapy was 52.5 Gy in 30 fractions (1.75 Gy per frac-
tion), over 6 weeks. Blood work was completed weekly
during the course of treatment.

The irradiated treatment volume was defined using
computed tomography-based planning. The gross tumour
volume (GTV) included the primary tumour and adjacent
grossly involved lymph nodes. Elective irradiation of
regional lymph nodes was not carried out. The clinical
target volume (CTV) consisted of the GTV plus a 0.5–1 cm
margin of adjacent tissue at risk for microscopic spread. In
some patients the CTV also included a 1 cm margin on the
most proximal 1.5 cm of the superior mesenteric artery and
the celiac artery, trimmed against anatomical boundaries,
with the aim of covering microscopic spread along peri-
nervous sheaths and autonomic ganglia. For postoperative
patients the CTV was individualised based on pathological
and surgical information, but included the preoperative
GTV, a 0.5 cm margin on the pancreaticojejunostomy and
hepaticojejunostomy sites, and a margin on the proximal
superior mesenteric artery and celiac artery as described
above. Before the availability of four-dimensional computed
tomography a 1 cm planning target volume (PTV) was used.
As of June 2007, four-dimensional computed tomography
became available. It was used to determine the magnitude
of target motion secondary to respiration for the creation of
an internal target volume. A 0.5–0.7 cm margin was created
around the internal target volume for the PTV. Radiation
therapy was delivered using megavoltage photons (6 MV
and 18 or 25 MV) with three-dimensional conformal
radiotherapy (most commonly a three-field beam arrange-
ment) up until January 2008 \((n = 59)\) and from that time
onwards with segmented intensity-modulated radio-
therapy \((n = 15)\).

**Evaluation and Follow-up**

Patients were assessed at 4–8 weeks after the comple-
tion of treatment with a clinical review and computed to-
mography scans of the chest, abdomen and pelvis. The
response to treatment was retrospectively categorised
based on this first post-treatment computed tomography
using the response criteria previously described by Brade
et al. \([10]\). Follow-up after treatment consisted of a clinical
review and computed tomography imaging, the frequency
of which was at the discretion of the treating clinician and
as driven by patient symptoms. The site of first metastasis
was documented based on imaging results.

**Statistical Analysis**

Overall survival was measured from the diagnosis date to
the date of death or last follow-up. Progression-free survival
(PFS) was calculated from the diagnosis date to the date of
progression (local or distant) or death. Local PFS and distant
PFS were calculated similarly. Survival probabilities for all
end points were calculated using Kaplan–Meier estimates.
Four patients at the last follow-up had unknown vital status
or missing death dates and were therefore censored. For the
patients with unresectable disease, a univariable and multivariable analysis was completed to assess the effect of
potential prognostic factors on local PFS and overall sur-
vival. The variables in the analysis included: GTV (as a
continuous variable and also dichotomised using the me-
dian value 48 cm\(^3\)), PTV, age at diagnosis, presence of a
biliary stent and delivered dose (52.5 versus <52.5 Gy). Differences in survival functions were examined using the Log-rank test. PTV was not included in the multivariable analysis due to the correlation with the GTV and because it was not significant on univariate analysis. Effects of variables on overall survival and local PFS were studied using Cox proportional hazard regression. All tests were two-sided with a significance level of 0.05.

Results

Patients and Treatment

After approval from the local Research Ethics Board, 90 patients were retrospectively identified to have started on the treatment protocol between March 2001 and August 2009. Of these, 74 patients were deemed unresectable, after being reviewed by an experienced hepatobiliary surgeon (n = 62) or at laparotomy (n = 12, who all went on to receive a palliative bypass procedure). The LAPC group also included 4/15 patients who had a Whipple's procedure upfront, but developed isolated local recurrence. One patient, initially deemed unresectable due to hepatic artery involvement, had a partial response to the treatment protocol and proceeded to a Whipple's procedure and is included in the resected population for analysis. All patients who were analysed in the resected population were considered to be at high risk of local recurrence with either positive (n = 10) or close margins (n = 2). Patient and tumour characteristics are shown in Table 1. As the treatment protocol was the same for the unresectable and the adjuvant patients, in the following description, toxicity is discussed for both groups together, but outcomes are discussed separately.

Induction Gemcitabine Chemotherapy for Unresectable and Adjuvant patients

All seven doses (and in six patients more than seven doses) of weekly gemcitabine were completed by 75.6% (n = 68) of patients. Four patients (4.4%) did not receive induction gemcitabine due to clinician’s preference and six patients (6.7%) received six doses, also due to clinician’s preference. The remaining 12 patients (13.3%) received between two and six doses for the following reasons: two patients stopped gemcitabine early due to stent complications, six due to progression and four due to toxicity. Toxicity included neutropenia (n = 3) or poor tolerance/decreased performance status (n = 1).

Re-imaging after Induction Gemcitabine for Unresectable and Adjuvant patients

Stable disease was seen in 64 patients (71.1%) on re-imaging after induction gemcitabine. Of this group, all patients went on to receive chemoradiotherapy, except for three patients. This was due to a gastrointestinal bleed in one patient, decreased performance status in another and prolonged pancytopenia in the third patient. One patient underwent neither repeat imaging nor chemoradiotherapy due to a deterioration in performance status. Evidence of progression on imaging was seen in 21 (23.3%) patients in the unresected group. Nine patients (10%) proceeded to chemoradiotherapy despite progression. Of these nine patients, local progression only (n = 6) or both local and distant progression (n = 3) was noted. As discussed above, four patients in the study did not receive induction chemotherapy and proceeded directly to definitive chemoradiotherapy. The adjuvant group are included in the figures above. All 12 patients treated in the adjuvant setting had no sign of progression after the induction gemcitabine.

Chemoradiotherapy for Unresectable and Adjuvant Patients — Toxicity

In total, 74 (82.2%) patients proceeded to chemoradiotherapy. Of these patients, 51 (68.9%) completed the

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<td>Patient and tumour demographics</td>
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<td>Female 34 (37.8%)</td>
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<td>GTV, gross tumour volume; PTV, planning target volume.</td>
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GTV range 10.9–180.3 |
| Median PTV | 365.1 |
| PTV range | 119.9–956.6 |
prescribed dose of 52.5 Gy. A reduced dose (≥45 Gy, but less than 52.5 Gy) was completed in 10.8% (n = 8) of the patients. In two patients this was a planned dose reduction (45 Gy in 25 fractions) due to concern about the dose to normal bowel. The other six patients stopped treatment early due to treatment toxicity (n = 5) or evidence of metastatic disease on imaging (n = 1). Fifteen patients (20.3%) received <45 Gy. This was due to treatment toxicity in 12 patients, stent complication in one patient, withdrawal of patient consent in one patient and secondary to a painful osteoporotic crush fracture in one patient. In total, 17 patients (22.9%) stopped chemoradiotherapy early secondary to treatment toxicity. Nausea, anorexia and fatigue were the most common causes for stopping treatment, whereas vomiting and diarrhoea were also noted in a smaller proportion of patients.

One patient (classified as stopping treatment early due to toxicity) died while having treatment (after receiving 40.3 Gy) due to a head injury after a fall. No imaging was available for review. The platelet count was mildly low (125 bil/l). Three patients died within 1 month of completing chemoradiotherapy and before re-imaging was carried out. One had chemoradiotherapy ceased at 31.5 Gy due to stent complications, one stopped treatment at 50.75 Gy due to nausea, diarrhoea and vomiting and the third patient completed treatment to 52.5 Gy. In the unresectable group, although there was a trend to larger a GTV and PTV in patients who stopped chemoradiotherapy early compared with those who completed treatment, the difference was not significant.

Three patients were documented to have had an upper gastrointestinal bleed. In one patient this occurred after completing seven doses of induction gemcitabine and before chemoradiotherapy. Another patient had a gastrointestinal bleed 2.8 years after completing treatment. This patient was noted to have oesophageal varices as the cause of the upper gastrointestinal bleed, but duodenal ulceration was also noted. The third patient had an upper gastrointestinal bleed 11 months after the completion of treatment while on gemcitabine for progression of local disease. All patients had grade 3 toxicity only.

Response after Chemoradiotherapy

Adjuvant Patients

No progression was noted on the first imaging in the 11 resected patients who were treated in the adjuvant setting.

Unresectable Patients

No complete responses were noted. One patient had a partial response and proceeded to a Whipple’s procedure as discussed above, and is included in the adjuvant analysis as the 12th patient. This was the only patient who proceeded to surgical resection after completing chemoradiotherapy. Forty-five (60.8%) patients had stable disease and 17 (22.9%) had progressive disease. Only three of these patients had isolated local progression, the remaining had metastatic disease alone (n = 8) or both local progression and metastatic disease (n = 6).

Additional Chemotherapy

Further chemotherapy after the described treatment protocol was at the discretion of the treating clinician. However, fewer than 10 patients were documented to have received further chemotherapy, with most managed with best supportive care alone after progression. Given the small numbers we did not analyse these patients separately.

Follow-up and Survival

Survival was calculated on an intention to treat basis, including the patients who did not proceed to chemoradiotherapy after the induction gemcitabine. The median follow-up of all 90 patients was 13.5 months (range 3.7–63.3 months).

Adjuvant Patients

The median overall survival time was 18.2 months (95% confidence interval 12.7–45.6) for the resected population (Figure 1). The overall survival rates at 1 and 2 years were 100 and 33.3% (95% confidence interval 10.3–58.8), respectively. At last follow-up, two patients were alive. The median PFS, median local PFS and median distant PFS were: 16.1 months (95% confidence interval 8.0–20.1), 16.5 months (95% confidence interval 10.6–20.1) and 16.2 months (95% confidence interval 8.0–37.0).

Unresectable Patients

The median overall survival time was 12.7 months (95% confidence interval 10.6–15.1) for the unresectable population (Figure 1). For the 62 patients who proceeded to chemoradiation after induction gemcitabine it was 14.5 months (95% confidence interval 11.9–16.7). Overall survival rates at 1 and 2 years were 53.6% (95% confidence

![Fig 1. Kaplan–Meier overall survival curves of locally advanced and resectable groups.](image-url)
interval 41.8–64.1) and 14.7% (95% confidence interval 7.8–23.7). The median PFS, median local PFS and median distant PFS were: 8.7 months (95% confidence interval 7.1–10.5), 9.6 months (95% confidence interval 8.7–11.3) and 10.5 months (95% confidence interval 7.6–11.8). For both the resected and unresectable patients the most common site of first metastasis was peritoneal disease, followed by liver metastases.

Univariable and Multivariable Analysis for Patients with Unresectable Locally Advanced Disease

Overall Survival

In univariable analysis, only GTV as a continuous variable had a significant effect on overall survival ($P = 0.04$). GTV dichotomised using the median value of 48 cm$^3$ was borderline significant ($P = 0.07$) with an improved median overall survival: 16.3 (95% confidence interval 11.4–20.3) months for GTV $\leq$ 48 cm$^3$ compared with 14.1 (95% confidence interval 10.4–16.1) months for GTV $> 48$ cm$^3$ (Figure 2). Delivered dose = 52.5 Gy was also borderline significant for improved overall survival ($P = 0.06$) compared with those patients receiving <52.5 Gy. PTV, age and the presence of a stent were not significant prognostic factors for overall survival.

In the multivariable analysis of overall survival, GTV (continuous, unit: 20 cm$^3$) remained a statistically significant prognostic factor ($P = 0.046$) with a hazard ratio of 1.18 (95% confidence interval 1.00–1.38) after adjusting for non-significant prognostic factors. The delivered dose of radiotherapy was not statistically significant on multivariable analysis.

Local Progression-free Survival

Potential prognostic factors identified above, excluding the presence of a biliary stent, were analysed in regards to local PFS. In the univariable analysis, GTV (both binary and continuous) and radiotherapy dose (<52.5 Gy versus 52.5 Gy) had significant effects on local PFS ($P = 0.015$, 0.03 and 0.02, respectively). GTV ($> 48$ versus $\leq 48$ cm$^3$) and radiotherapy dose (<52.5 Gy versus 52.5 Gy) remained statistically significant in the multivariable analysis, with $P = 0.008$ and $P = 0.03$ and a hazard ratio of 2.35 (95% confidence interval 1.25–4.42) and 1.93 (95% confidence interval 1.05–3.53), respectively. Patients with a GTV $> 48$ cm$^3$ had a median local PFS of 10.4 months (95% confidence interval 8.7–11.6), whereas those with a GTV $\leq 48$ cm$^3$ had a median local PFS of 12.7 months (95% confidence interval 7.8–17.3) (Figure 3).

Discussion

This retrospective study supports our previous phase I–II study conclusion that the treatment protocol of induction gemcitabine followed by chemoradiotherapy with biweekly gemcitabine is effective and tolerable. The induction gemcitabine selected 17.8% ($n = 16$) of patients who would be unlikely to benefit from chemoradiotherapy, due to early progressive disease ($n = 12$) or performance status deterioration. These patients were therefore spared the potential toxicity of chemoradiotherapy. In only one patient was the reason for not proceeding to chemoradiotherapy secondary to gemcitabine toxicity. For the 82.2% ($n = 74$) of patients who proceeded to chemoradiotherapy after the induction gemcitabine, treatment was tolerable, with 79.7% completing $\geq 45$ Gy. Due to treatment toxicity, 22.9% of patients stopped treatment, most commonly as a result of anorexia, nausea and fatigue. However, the retrospective nature of this study meant data regarding treatment toxicity were incomplete and no formal quality of life data

Fig 2. Kaplan–Meier overall survival curves of gross tumour volume (GTV) $> 48$ cm$^3$ and GTV $\leq 48$ cm$^3$ in locally advanced patients.

Fig 3. Kaplan–Meier local progression-free survival curves of gross tumour volume (GTV) $> 48$ cm$^3$ and GTV $\leq 48$ cm$^3$ in locally advanced patients.
were collected, limiting our ability to comment on these important factors.

The survival results of the locally advanced group (median 12.7 months) are comparable with other studies where gemcitabine was used as a radiosensitiser, with the overall median survival in these phase I–II studies being 7.9–14.5 months [10,11,16–26]. The median survival of patients with unresectable disease who proceeded to chemoradiotherapy was 14.5 months; 14.5% (n = 9) of these patients had evidence of progression after the induction gemcitabine. A study of 16 patients with unresectable disease given induction chemotherapy of gemcitabine with or without capcetabine followed by chemoradiation with concurrent weekly gemcitabine reported a median survival of 15.3 months compared with 9.2 months for 26 patients treated with chemotherapy alone [27]. The study in this paper was larger and the chemotherapy standardised to gemcitabine alone, which is given twice weekly as opposed to weekly, but has a similar median survival. However, the results of the LAP 07 phase III trial comparing chemoradiotherapy and chemotherapy after induction chemotherapy (with or without erlotinib) have recently been presented and published in abstract form [9] and the median survival was similar in both arms (15.2 versus 16.4 months). The study questions the benefit of radiation in addition to chemotherapy for patients with unresectable disease. The radiation details (e.g. volume irradiated) have yet to be published and we await the final manuscript with interest. If chemotherapy alone becomes the standard of care for patients with locally advanced disease, there may still be a role for chemoradiation similar to that described in this paper for patients who do not respond or subsequently locally progress.

In patients with locally advanced disease, unreparable and multivariable analysis revealed GTV to be significantly correlated with overall survival. In patients with a GTV > 48 cm³ outcomes were poor and because 22.9% of patients will suffer treatment toxicity resulting in the cessation of treatment, careful consideration should be given before recommending treatment for patients with a GTV > 48 cm³. A radiotherapy dose of less than 52.5 Gy was also associated with poorer local PFS.

In the locally advanced group, the median local PFS of 9.6 months was similar to the median distant PFS of 10.5 months. Likewise, in the resected group the median local PFS and median distant PFS were similar; 16.5 months and 16.2 months, respectively. This highlights the need for improvements in both systemic and local treatments. FOLFIRINOX, recently shown to double 1 year survival rates in the metastatic population when compared with gemcitabine [28], is a promising advancement in systemic treatment and may have a role as an induction chemotherapy protocol in future trials for localised pancreatic cancer. With regards to lowering locoregional failure rates, a variety of approaches are being investigated, including stereotactic body radiotherapy (SBRT), protons [29,30] and neoadjuvant treatment. Although SBRT has the advantage of decreased overall treatment time for patients, there is potential for serious toxicity given the often intimate relationship of the tumour to the duodenum and/or stomach. Studies have noted that late gastrointestinal toxicity rates (>grade 3), such as duodenal ulceration, bleeding or perforation, vary between 5 and 38% without significant improvements in median survival (5.7–11.8 months) [21,31–34] compared with conventional chemoradiation protocol. However, local control rates seem to be superior at 75–94% [31,33,35]. A retrospective series [36] has shown promise using induction gemcitabine to select out patients with early metastatic disease before SBRT, documenting a median overall survival of 20 months in the patients that subsequently proceeded to SBRT. Future developments in systemic agents and refinement of radiotherapy techniques, including attention to duodenal tolerance, may improve locoregional control.

**Conclusion**

This series confirms a similar efficacy of this treatment strategy in a larger series and in a standard practice setting. However, there is a need to improve both local and systemic control via further investigation into newer drug regimens and radiation techniques. Caution should be used in treating patients with large GTVs.

**Acknowledgement**

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**References**


