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Concurrent high-dose intensity-modulated radiotherapy and chemotherapy for unresectable locally advanced and metastatic pancreatic cancer: a pilot study

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Original Article

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Abstract

Aim: To evaluate the efficacy of concurrent chemotherapy and high-dose (≥55 Gy) intensity-modulated radiotherapy (CCIMRT) in comparison with chemotherapy alone and intensity-modulated radiotherapy (IMRT) alone for unresectable locally advanced or metastatic pancreatic cancer.
Methods: Forty-six patients with pancreatic cancer undergoing CCIMRT ($n = 17$), chemotherapy alone ($n = 16$) or IMRT alone ($n = 13$) were analysed. Overall survival (OS), locoregional progression-free survival (LRPFS) and gastrointestinal toxicities were evaluated. The median radiation dose was 60 Gy (range, 55–60) delivered in a median of 25 fractions (range, 24–30). Gemcitabine (GEM) alone, GEM + S-1, S-1 alone, FOLFIRINOX and GEM + nab-paclitaxel were used in CCIMRT and chemo-monotherapy.
Results: The 1-year OS rate was 69% in the CCIMRT group, 27% in the chemotherapy group and 38% in the IMRT group ($p = 0{\cdot}12$). The 1-year LRPFS rate was 73, 0 and 40% in the 3 groups, respectively ($p = 0{\cdot}012$). Acute Grade ≥ 2 gastrointestinal toxicity (nausea, diarrhea) was observed in 12% (2/17) in the CCIMRT group, 25% (4/16) in the chemotherapy group and 7·7% (1/13) in the IMRT group ($p = 0{\cdot}38$). Late Grade 3 gastrointestinal bleeding was observed in 6·3% (1/16) in the chemotherapy group.
Conclusion: High-dose CCIMRT yielded acceptable toxicity and favorable OS and LRPFS.

Introduction

Surgical resection, if applicable, is the first choice of treatment for pancreatic cancer. However, only about 20–25% of all pancreatic cancer patients are resectable.[1,2] Standard management of unresectable pancreatic cancer has not been established. It has been reported that the median survival time (MST) with best supportive care is less than 6 months in patients with unresectable locally advanced or metastatic pancreatic cancer.[3,4] Chemotherapy, radiotherapy and chemoradiotherapy may be conceivable options of treatment for unresectable pancreatic cancer. However, the superiority of chemoradiotherapy over chemotherapy alone remains controversial; two studies suggested the superiority of chemoradiation over chemotherapy alone,[5,6] whereas others did not.[7–10] A reason why chemoradiotherapy has not been proven to be definitely superior to chemotherapy alone may be the use of relatively low doses of radiation therapy. Since the pancreas is surrounded by radiosensitive gastrointesitinal tracts, tolerable doses of 50–54 Gy or less have been employed in previous studies.[11,12] In view of the relative radioresistance of pancreatic cancer, higher doses may be desirable to definitely improve local control.[13,14]

Recently-established intensity-modulated radiation therapy (IMRT) enables delivery of higher doses (≥55 Gy) to the pancreatic tumour while administering tolerable doses (<50 Gy) to the gastrointestinal tract included in the target volume. This can be achieved especially using the simultaneous integrate boost (SIB) technique. To our knowledge, however, IMRT has not yet been employed in prospective studies comparing chemoradiotherapy with chemotherapy. To properly evaluate the role of radiotherapy in the treatment of unresectable pancreatic cancer, it seems desirable to use IMRT in a prospective study.

We have been using IMRT with helical tomotherapy for the treatment of pancreatic cancers in combination with systemic chemotherapy. Using the SIB technique, doses of 55–60 Gy with a daily dose of 2–2·5 Gy have been focussed onto tumour regions, while the dose to the gastrointestinal tract was kept to be lower than 50 Gy. The standard dose to the tumour was 60 Gy delivered preferably in 25 fractions. Our policy was to use concurrent chemotherapy and high-dose IMRT (CCIMRT) even in patients with distant metastasis; metastatic tumours were

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included in the treatment field whenever possible. The purpose of the present study was to evaluate the outcome of CCIMRT. For comparison, patients treated with chemotherapy or radiotherapy alone were also analysed.

Materials and Methods

Patient characteristics

The subjects of this study were patients histologically or clinically diagnosed with pancreatic cancer who received CCIMRT using helical tomotherapy at our hospital between May 2008 and December 2019. For reference, patients who received chemotherapy or IMRT alone during the same period were also analysed. Other eligibility criteria were: (1) no previous treatment; (2) primary case and (3) unresectable tumour. Generally, unresectable pancreatic cancer was defined as a tumour having distant metastasis to other organs and/or a tumour having invasion to or contact with the major arteries, portal vein and superior mesenteric vein, also taking patient age into consideration. A total of 46 patients were treated: 17 by CCIMRT, 16 by chemotherapy and 13 by IMRT. This study was approved by the institutional review board. Informed consent was obtained from all patients.

Chemotherapy

For CCRT, the following regimens were employed: intravenous (iv) gemcitabine (GEM, 1000 mg/m^2, day 1 and 8) + oral S-1 (60 mg/m^2, day 1–14) repeated every 3 weeks; oral S-1 (80 mg/m^2, day 1–14) repeated every 3 weeks; and iv GEM (1000 mg/m^2, day 1, 8 and 15) plus nab-paclitaxel (nab-PTX, 125 mg/m^2, day 1, 8 and 15) repeated every 4 weeks (GnP). For chemotherapy alone, the following regimens were employed: GnP; iv oxaliplatin (85 mg/m^2, day 1) + levofolinate (200 mg/m^2, day 1) + irinotecan (180 mg/m^2, day 1) + 5-fluorourcil (400 mg/m^2 single shot and 2400 mg/m^2 over 24 hours, day 1) repeated every other week (FOLFIRINOX) and GEM monotherapy (1000 mg/m^2, day 1, 8 and 15) repeated every 4 weeks. Dose reduction by 20% and elongation of the chemotherapy interval by 1–2 weeks were considered in cases of severe toxicity and/or high age.

Radiation therapy

IMRT was delivered with the helical mode of TomoTherapy Hi-Art or HDA system (Accuray Inc., Sunnyville, CA, USA). Patients were fixed with the BodyFix system (Medical Intelligence, Schwabmuenchen, Germany) and scanned for treatment planning with a 4- or 16-row multidetector computed tomography (CT) with a slice thickness of 2·5 mm under shallow breathing and breath holding during the inspiratory and expiratory phases. Subsequent planning was made with the TomoTherapy planning station. Contouring was performed on non-contrast CT images with fusion or with reference to contrast-enhanced CT and PET-CT images according to the previous study.[15] The gross tumour volume (GTV) was the primary pancreatic tumour, lymph node metastasis, and whenever possible, liver metastasis. The GTVs during the three phases were superimposed to create GTV-all. The clinical target volume (CTV) was the GTV-all plus 5-mm margins and also included appropriate ranges of the para-aortic lymph node regions over the plexus region. The planning target volume 1 (PTV1) was the CTV plus anteroposterior and lateral 5-mm margins and craniocaudal 10-mm margins. PTV2 was GTV-all plus 3–5-mm margins in all directions. The SIB technique was used to deliver different doses to PTV1 and PTV2.

Typically, the prescribed doses to 50% of PTV 1 and PTV2 were 50 and 60 Gy, respectively, in 25 fractions. Depending on the size of PTV, 24 or 30 fractions were also used, and 55 Gy in 25 fractions was also used in the CCIMRT and IMRT-alone groups. Planning dose constraints for organs at risk are shown in Table 1. The maximum dose to the gastrointestinal tract was set to be below 50 Gy.

Table 1. Dose constrains for organs at risk

Organ	Constraint (Dmax)	Other constraints
Stomach	<50 Gy	V10Gy < 10 cc
Duodenum	<50 Gy	V10Gy < 10 cc
Spinal cord	<30 Gy	V10Gy < 10 cc
Kidney	<50 Gy	V20Gy < 20 cc
Colon	<50 Gy	V10Gy < 10 cc
Liver	<50 Gy	Dmean < 30 Gy

Follow-up evaluation

All patients were followed at 1- to 3-month intervals with physical examination and CT. Upon this analysis, special attention was paid to the locoregional status. A 20% or greater increase in the tumour diameter or appearance of a new regional lesion was regarded as locoregional failure. Acute gastrointestinal toxicity, including nausea and vomiting, diarrhea and abdominal pain, and chronic gastrointestinal toxicity were evaluated according to the Common Terminology Criteria for Adverse Events Version 4.0.

Statistical analysis

The Chi-square or Mann–Whitney U test was used to examine differences in patient characteristics and gastrointestinal toxicities among the CCIMRT, chemotherapy-alone, and IMRT-alone groups. Overall survival (OS) was defined as the period from the start of treatment to the date of death or last follow-up. The Kaplan–Meier method was used to estimate OS and locoregional progression-free survival (LRPFS). The log-rank test was used for comparisons of OS and LRPFS. All statistical tests were two-sided. Statistical significance was defined with a p-value < 0·05. All statistical analyses were performed using Mac Statistical Analysis Version 3.0 (ESUMI Co., Ltd., Tokyo, Japan).

Results

Patient and tumour characteristics

Table 2 shows characteristics of the patients, treatments and tumours in the 3 groups. In the CCIMRT group, the schedule of 60 Gy delivered in 25 fractions was employed in 11 patients (65%). The schedule of 55 Gy in 25 fractions was used in four patients (24%) in the CCIMRT group and six (46%) in the IMRT-alone group. The tumour marker data were lacking in two patients.

Treatment outcome

All but one patient were followed until death, and the remaining one patient was alive at 14·5 months at the time of this analysis. Figure 1 shows OS curves for the three groups. The median survival time (MST) was 15 months in the CCIMRT group and 9 months in

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Table 2. Patient, tumour and treatment characteristics

Characteristics	CCIMRT	Chemotherapy	IMRT	*P*
Patient number	17	16	13	
Age (years) median, range	68, 52–83	71, 40–81	72, 40–87	0·93
Gender male/female	10/7	11/5	8/5	0·83
Performance status 0, 1/2	13/4	10/6	12/1	0·17
Tumour location head, uncus/body, tail	5/12	11/5	7/6	0·83
Tumour size (cm) median, range	4·2, 2·0–5·0	3·6, 2·0–13·4	3·1, 1·8–5·2	0·057
Distant metastasis +/−	5/12	11/5	8/5	0·056
Pretreatment CA19-9 (IU/ml) median, range	619, 15–4488	2620, 1·5–46098	401, 24–21480	0·16
Pretreatment CEA (ng/ml) median, range	3·6, 1·5–23	5·8, 3·4–37·5	3·9, 1·8–66·2	0·073
Radiation dose (Gy) median, range	60, 55–60	–	56·7, 55–60	
Radiation fraction number median, range	25, 24–30	–	25, 25–30	
Chemotherapy				
n (course: median, range)				
GEM + S-1	2	7 (4, 3–8)		
S-1	8		–	
GnP	4	6 (4·5, 3–7)		
FOLFIRINOX		2 (1, 1)		
GEM	3	1 (5, 5)		

GEM, gemcitabine; GnP, gemcitabine + nab-paclitaxel; FOLFIRINOX, oxaliplatin + levofolinate + irinotecan + 5-fluorouracil.

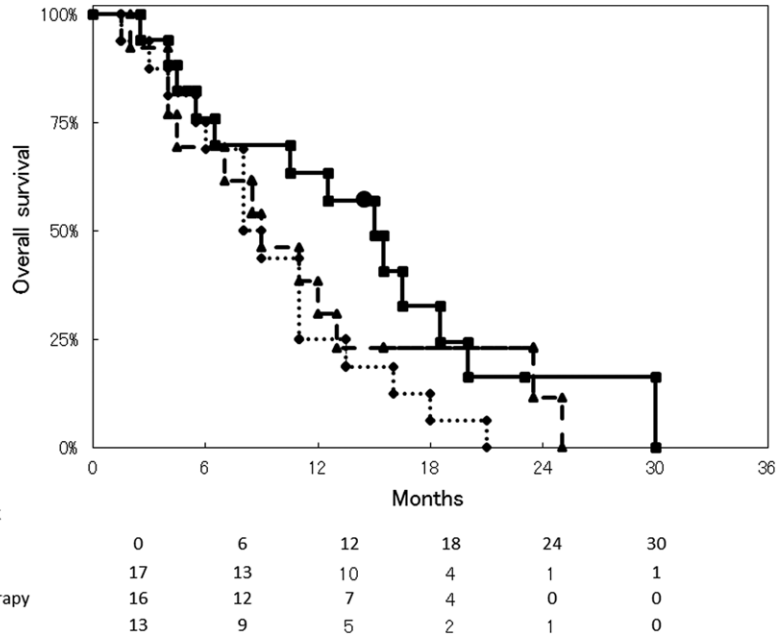

Figure 1. Overall survival curves for the CCIMRT group (solid line, $n = 17$), chemotherapy group (dotted line, $n = 16$) and IMRT group (broken line, $n = 13$). $p = 0{\cdot}12$.

the chemotherapy and IMRT groups ($p = 0{\cdot}12$). The 1-year OS rate was 69% in the CCIMRT group, 27% in the chemotherapy group and 38% in the IMRT group. The 2-year OS rate was 20, 0 and 12% in the three groups, respectively. In nine patients of the CCIMRT group who received GEM-containing chemotherapy, the MST was 16·5 months, and the 1- and 2-year OS rates were 78 and 16%, respectively. In six non-metastatic patients of the CCIMRT group who received GEM-containing chemotherapy, the MST was 20 months, and the 1- and 2-year OS rates were 83 and 30%, respectively.

Figure 2 shows OS curves according to the presence/absence of distant metastasis at diagnosis for the three groups. In patients without distant metastasis, the MST was 20 months in the CCIMRT group, 13·5 months in the chemotherapy group, and

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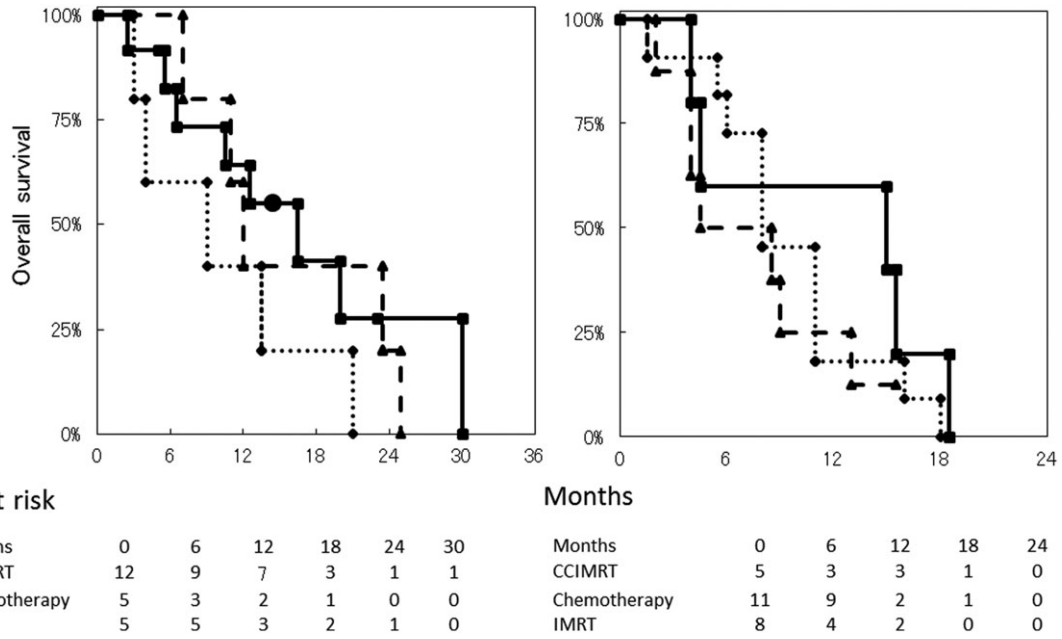
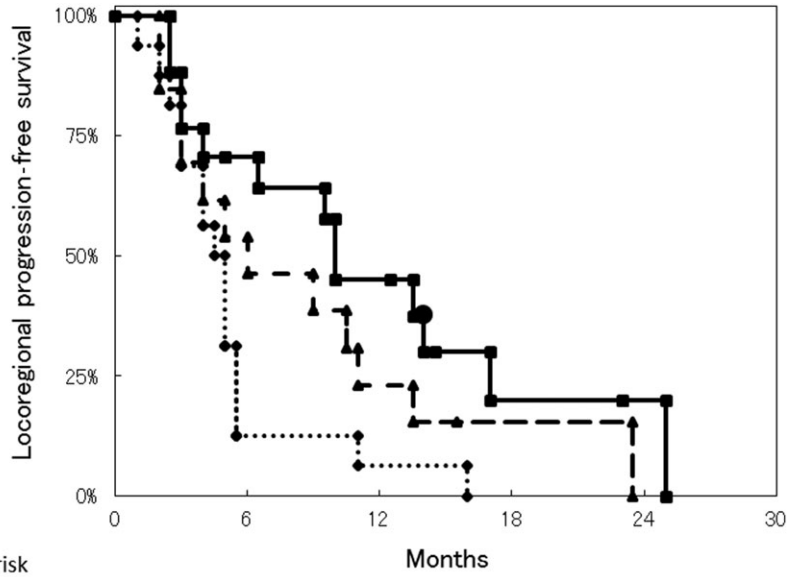


No. at risk

Months	0	6	12	18	24	30
CCIMRT	12	9	7	3	1	1
Chemotherapy	5	3	2	1	0	0
IMRT	5	5	3	2	1	0

Months	0	6	12	18	24
CCIMRT	5	3	3	1	0
Chemotherapy	11	9	2	1	0
IMRT	8	4	2	0	0

Figure 2. Overall survival curves for the CCIMRT group (solid line), chemotherapy group (dotted line) and IMRT group (broken line). Left panel: patients without distant metastasis at diagnosis ($n = 12$, 5 and 5, respectively; $p = 0{\cdot}38$). Right panel: patients with distant metastasis ($n = 5$, 11 and 8, respectively; $p = 0{\cdot}43$).



No. at risk

Months	0	6	12	18	24	30
CCIMRT	17	11	6	2	1	0
Chemotherapy	16	2	1	0	0	0
IMRT	13	7	3	1	0	0

Figure 3. Locoregional progression-free survival curves for the CCIMRT group (solid line, $n = 17$), chemotherapy group (dotted line, $n = 16$), and IMRT group (broken line, $n = 13$). $p = 0{\cdot}012$.

12 months in the IMRT group ($p = 0{\cdot}38$). The 1-year OS rate was 73, 53 and 60%, respectively, and the 2-year OS rate was 37, 0 and 20%, respectively. In patients with distant metastasis at diagnosis, the MST was 15 months in the CCIMRT group, 8·5 months in the chemotherapy group, and 4·5 months in the IMRT group ($p = 0{\cdot}43$). The 1-year OS rate was 60, 18 and 25%, respectively.

Figure 3 shows LRPFS curves for the three groups. The median time to locoregional progression was 17 months in the CCIMRT group, 5·5 months in the chemotherapy group and 10·5 months in the IMRT groups ($p = 0{\cdot}012$). The 1-year LRPFS rate was 73, 0 and 40% in the three groups, respectively.

Table 3 shows the results of univariate analysis of potential prognostic factors in all 46 patients. The presence of distant metastasis at diagnosis, pretreatment high CA19-9 level (above median) and pretreatment high CEA level (above normal range) were associated with worse OS and LRPFS.

Acute Grade 2 gastrointestinal toxicity (nausea, diarrhea) was observed in 12% (2/17) of the patients in the CCIMRT group,

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Table 3. Univariate analysis of all 46 patients

Factor	*n*	1-year OS (%)	*P*	1 year LRPFS (%)	*P*
Age >/≤70 (years)	23/23	40/34	0·58	26/29	0·76
Gender male/female	29/17	46/34	0·94	24/36	0·96
Performance status 0, 1/2	35/11	51/27	0·26	34/18	0·13
Tumour location					
Head, uncus/body, tail	24/22	41/43	0·78	22/33	0·63
Tumour size >/≤3·7 cm	22/24	34/40	0·29	29/27	0·69
Distant metastasis +/–	24/22	29/58	0·003	13/47	0·003
Pretreatment CA19-9					
>/≤740 U/ml	21/23	20/63	0·001	10/48	0·00002
Pretreatment CEA					
>/≤5·0 ng/ml	19/25	28/54	0·014	17/39	0·015

19% (3/16) in the chemotherapy group and 7·7% (1/13) in the IMRT group. Acute Grade 3 diarrhea was observed in 6·3% (1/16) in the chemotherapy group, and late Grade 3 gastrointestinal bleeding was observed in 6·3% (1/16) in the chemotherapy group. No other Grade 3 or higher toxicity was observed. The difference in the Grade ≥ 2 acute gastrointestinal toxicity among the three groups was not significant ($p = 0·38$).

Discussion

Pancreatic cancer is not a radiosensitive tumour, and conventional radiation therapy with doses of 50–54 Gy has not been so useful to improve the prognosis of the patients. However, delivering higher doses may be beneficial in a proportion of patients who do not develop metastasis at an early period. A method to deliver a high dose is intraoperative radiation therapy.[14,16,17] By delivering a single high dose (25–30 Gy) in addition to external beam radiotherapy, better local control was reported, and also cure has been reported in some patients.[17,18] However, intraoperative radiotherapy is now not widely used because of the limitations in facilities using this modality. The use of stereotactic body radiotherapy (SBRT) may be an alternative approach. By using SBRT in combination with GEM chemotherapy, median survival times of 12 months or longer are reported.[19,20] However, the margins need to be narrow to protect the gastrointestinal tract, and so marginal recurrence may be a concern when SBRT is used alone. Instead, IMRT may be a more feasible modality to reasonably deliver high radiation doses. There have been reports on the use of IMRT for pancreatic cancer, but in most studies, the administered doses were similar to those used in conventional radiotherapy or were only modestly increased.[21–25] Concurrent IMRT and chemotherapy has been reported feasible,[25] but IMRT with a high dose, as defined by the biological effective dose with an α/β ratio of 10 Gy (BED_{10}) > 70 Gy,[12] has been scarcely reported.[5,8–10] Our present study has shown the feasibility of concurrent high-dose IMRT and chemotherapy with acceptable toxicities.

This study mainly used 60 Gy in 25 fractions to PTV2; the BED_{10} was 74·4 Gy. The dose to PTV1 was mainly 50 Gy, and the dose to the gastrointestinal tract was kept at less than 50 Gy in 25 fractions using the SIB technique. Still higher doses may be delivered when the treatment volume is limited to the primary tumour,[22,26] but doing this may allow early regional recurrence. Therefore, we think our method and doses of IMRT with the SIB technique are reasonable to combine with concurrent chemotherapy.

Our study is retrospective and each treatment was mostly allocated at the discretion of attending physicians. Therefore, the results of the CCIMRT, chemotherapy, and IMRT groups cannot be compared; however, LRPFS in the CCIMRT group seemed to be favourable, suggesting the benefit of high radiation doses in combination with chemotherapy on locoregional control. The outcomes of the CCIMRT group compare favorably with those of prospective studies of chemoradiation therapy.[5–9] From the results of this study, prospective randomised studies of CCIMRT versus chemotherapy alone seem to be warranted.

In this study, patients with distant metastases were also treated with radiation therapy. Metastatic tumours were included in the treatment volume whenever possible. Using helical tomotherapy, such a treatment is readily afforded. Takaoka et al.[27] treated chemorefractory multiple liver metastases with helical tomotherapy and obtained prolongation of OS. In future studies, it seems that Stage IV patients with oligometastatic tumours can be regarded as candidates for IMRT. CCIMRT covering the primary tumour and oligometastatic lesions should be considered.

There are many limitations in this study. In addition to the retrospective study design and small patient number, selection criteria for treatment choice were not defined. More than half of the patients had metastatic disease. The three groups of patients had great heterogeneity even within the group of CCIMRT. Although our policy of delivering high doses in combination with chemotherapy was uniform, the dose fractionation schedules slightly varied with patients. So, prospective studies with more patients are needed to definitely show that our approach is promising. Although chemotherapy regimens were various, it was suggested that a GEM-based regimen could be combined with high-dose IMRT, and our preliminary results appear promising. In further studies, we plan to continue this treatment with a fixed schedule of 60 Gy in 25 fractions to the tumour and a GEM-based chemotherapy regimen.

Conclusion

This study demonstrated the feasibility of concurrent high-dose IMRT and chemotherapy. The preliminary results seem encouraging. Future studies incorporating high-dose IMRT into treatment

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protocols for unresectable as well as oligometastatic pancreatic caners seem to be warranted.

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Conflict of Interest. None.

Ethical Standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation Hokuto Hospital and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees Hokuto Hospital. Informed consent was obtained and chart reviews were performed after approval by the ethics committee of Hokuto Hospital.

References

1. Willett C G, Czito B G, Bendell J C et al. Locally advanced pancreatic cancer. J Clin Oncol 2005; 23: 4538–4544.
2. Krishnan S, Rana V, Janjan N A et al. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. Cancer 2007; 110: 47–55.
3. Tsavaris N, Tentas K, Tzivras M et al. Combined epirubicin, 5-fluorouracil and folinic acid vs no treatment for patients with advanced pancreatic cancer: a prospective comparative study. J Chemother 1998; 10: 331–337.
4. Shibamoto Y, Nishimura Y, Abe M. Intraoperative radiotherapy and hyperthermia for unresectable pancreatic cancer. Hepato-Gastroenterology 1996; 43: 326–332.
5. Loehrer P J Sr, Feng Y, Cardenes H et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. J Clin Oncol 2011; 29: 4105–4112.
6. Gastrointestinal Tumor Study Group. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. J Natl Cancer Inst 1988; 80: 751–755.
7. Chauffert B, Mornex F, Bonnetain F et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. Ann Oncol 2008; 19: 1592–1599.
8. Klaassen D J, MacIntyre J M, Catton G E et al. Treatment of locally unresectable carcinoma: a randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil—an Eastern Cooperative Oncology Group study. J Clin Oncol 1985; 3: 373–378.
9. Hazel J J, Thirlwell M P, Huggins M et al. Multi-Drug chemotherapy with and without radiation for carcinoma of the stomach and pancreas: a prospective randomized trial. J Can Assoc Radiol 1981; 32: 164–165.
10. Hammel P, Hugel F, van Laethem J L et al. Effect of Chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 randomized clinical trial. JAMA 2016; 315: 1844–1853.
11. Blakaj A, Stein S M, Khan S A et al. Review and current state of radiation therapy for locally advanced pancreatic adenocarcinoma. J Gastrointest Oncol 2018; 9: 1027–1036.
12. Jaoude J A, Kouzy R, Nguyen N D et al. Radiation therapy for patients with locally advanced pancreatic cancer: evolving techniques and treatment strategies. Curr Prob Cancer 2020. doi: 10.1016/j.currproblcancer.2020.100607.
13. Shibamoto Y, Kubota T, Kishii K et al. Radiosensitivity of human pancreatic cancer cells in vitro and in vivo, and the effect of a new hypoxic cell sensitizer, doranidazole. Radiother Oncol 2000; 56: 265–270.
14. Shibamoto Y, Manabe T, Baba N et al. High dose, external beam and intraoperative radiotherapy in the treatment of resectable and unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys 1990; 19: 605–611.
15. Shibamoto Y, Naruse A, Fukuma H et al. Influence of contrast materials on dose calculation in radiotherapy planning using computed tomography for tumors at various anatomical regions: a prospective study. Radiother Oncol 2007; 84: 52–55.
16. Shibamoto Y, Manabe T, Ohshio G et al. High-Dose intraoperative radiotherapy for unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys 1996; 34: 57–63.
17. Karasawa K, Sunamura M, Okamoto A et al. Efficacy of novel hypoxic cell sensitiser doranidazole in the treatment of locally advanced pancreatic cancer: long-term results of a placebo-controlled randomised study. Radiother Oncol 2008; 87: 326–330.
18. Shibamoto Y, Sugie C, Ito M et al. The Japanese experiences with hypoxia-targeting pharmacoradiotherapy: from hypoxic cell sensitizers to radiation-activated prodrugs. Expert Opin Pharmacother 2004; 5: 2459–2467.
19. Gurka M K, Collins S P, Slack R et al. Stereotactic body radiation therapy with concurrent full-dose gemcitabine for locally advanced pancreatic cancer: a pilot trial demonstrating safety. Radiat Oncol 2013; 8: 44.
20. Herman J M, Chang D T, Goodman K A et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. Cancer 2015; 121: 1128–1137.
21. Wang Z, Ren Z G, Ma N Y et al. Intensity modulated radiotherapy for locally advanced and metastatic pancreatic cancer: a mono-institutional retrospective analysis. Radiat Oncol 2015; 10: 14.
22. Nakamura A, Hiraoka M, Itasaka S et al. Evaluation of dynamic tumor-tracking intensity-modulated radiotherapy for locally advanced pancreatic cancer. Sci Rep 2018; 8: 17096.
23. Goto Y, Nakamura A, Ashida R et al. Clinical evaluation of intensity-modulated radiotherapy for locally advanced pancreatic cancer. Radiat Oncol 2018; 13: 118.
24. Oh E S, Kim T H, Woo S M et al. Effectiveness and feasibility of concurrent chemoradiotherapy using simultaneous integrated boost-intensity modulated radiotherapy with and without induction chemotherapy for locally advanced pancreatic cancer. Radiat Oncol J 2018; 36: 200–209.
25. Huguet F, Hajj C, Winston C B et al. Chemotherapy and intensity-modulated radiation therapy for locally advanced pancreatic cancer achieves a high rate of R0 resection. Acta Oncol 2017; 56: 384–390.
26. De Felice F, Benevento I, Bulzonetti N et al. Hypofractionated intensity-modulated radiotherapy in locally advanced unresectable pancreatic cancer: a pilot study. Curr Prob Cancer 2019; 43: 495–503.
27. Takaoka T, Shibamoto Y, Murai T et al. Helical tomotherapy for chemo-refractory multiple liver metastases. Cancer Med 2019; 8: 7594–7602.

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