Hong Kong J Radiol. 2017;20:303-11 | DOI: 10.12809/hkjr1716861

REVIEW ARTICLE

Stereotactic Body Radiotherapy for Pancreatic Cancer

CL Chiang[1,2,3], CSY Yeung[3], MYP Wong[4], VWY Lee[3], VHF Lee[1,2], FAS Lee[3], FCS Wong[3]

[1]Department of Clinical Oncology, The University of Hong Kong, Pokfulam, Hong Kong; [2]Department of Clinical Oncology, The University of Hong Kong–Shenzhen Hospital, Shenzhen, China; [3]Department of Clinical Oncology, Tuen Mun Hospital, Tuen Mun, Hong Kong; [4]Department of Medical Physics, Tuen Mun Hospital, Tuen Mun, Hong Kong

ABSTRACT

Despite advances in surgical, radiation and systemic therapy, the prognosis of pancreatic cancer remains poor. Most patients are not amendable to curative surgical resection at presentation. Chemo-radiotherapy is the standard of care for locally advanced pancreatic cancer, but its local control is poor. Stereotactic body radiotherapy (SBRT) is a viable therapeutic option to maximise local control with a tolerable side-effect profile. It enables precise delivery of high-dose radiation over a short period (typically 1-5 days) and leads to better local control, disease outcome, and symptom palliation. SBRT can also be applied in neoadjuvant, adjuvant, or re-irradiation treatment. We review the technology, clinical application, and future direction of SBRT for treatment of pancreatic cancer.

Key Words: *Pancreatic neoplasms; Radiosurgery*

中文摘要

胰腺癌的立體定向放射治療

蔣子樑、楊善如、黃然柏、李蘊恩、李浩勳、李安誠、黃志成

雖然手術、放療和全身治療有所進步，但胰腺癌的預後仍然很差。大多數患者在入院時無法耐受手術切除。化放療是局部晚期胰腺癌的標準治療方案，但局部控制較差。立體定向放射治療（SBRT）是能提供最大局部控制的可行選擇，而其副作用是可耐受的。它能夠在短時間內（通常為1-5天）精確地輸送高劑量輻射，並導致更好的局部控制、疾病結果和症狀緩解。SBRT也可用於新輔助治療、輔助治療或再照射治療。我們回顧SBRT治療胰腺癌的技術、臨床應用和未來發展方向。

INTRODUCTION

According to the 2015 Hong Kong Cancer Registry report, pancreatic cancer ranked number four in cancer mortality, and its incidence was steadily rising, with 766 new cases in 2015.[1] Despite advances in surgical techniques, systemic treatment and molecular understanding, the prognosis of pancreatic cancer remains dismal, with a 5-year overall survival (OS)

Correspondence: *Dr CL Chiang, Department of Clinical Oncology, The University of Hong Kong, 1/F, Professorial Block, Queen Mary Hospital, 102 Pokfulam Road, Pokfulam, Hong Kong.*
Email: chiangcl@hku.hk

Submitted: 19 Feb 2017; Accepted: 2 May 2017.

Disclosure of Conflicts of Interest: All authors have disclosed no conflicts of interest.

of 6%.[2] Surgical resection is the standard of care, but only one-fifth of patients are suitable candidates owing to local invasion of tumour or metastasis. Even after resection, the 5-year survival is only 20% to 30%.[3] The incidence of local recurrence has been reported to be 20% to 60%.[4] In patients with unresectable locally advanced pancreatic cancer (LAPC), the treatment goal is local control, as complications such as pain and obstruction may severely impair quality of life. In an autopsy study, 30% of patients with pancreatic cancer died of local disease with few or no metastasis.[5]

The role of chemoradiotherapy (CRT) in treatment of LAPC remains controversial. The local failure rate has been reported to be 30% to 60% in patients with LAPC treated with CRT.[3,4] Nonetheless, both the Gastrointestinal Tumor Study Group 9283 study and the Eastern Cooperative Oncology Group 4201 study have reported improved OS after CRT, compared with chemotherapy alone.[6,7] Also, the Groupe Coopérateur Multidisciplinaire en Oncologie reported an increase in OS among patients who received both chemotherapy and CRT, compared with chemotherapy alone.[8] However, the Federation Francophone de Cancérologie Digestive study reported inferior OS and worse toxicity with CRT, compared with chemotherapy.[9] In a prospective randomised phase 3 study (LAP07), 442 patients with LAPC were randomised to receive gemcitabine or gemcitabine plus erlotinib, and then after 4 months, 269 of patients with local control were subsequently randomised to receive CRT or additional 2 months of chemotherapy.[10] After a median follow-up of 36.7 months, CRT and chemotherapy alone achieved comparable OS (15.2 months vs. 16.5 months, $p = 0.83$), although CRT reduced the rate of local progression (32% vs. 46%, $p = 0.03$).[10]

There are several drawbacks in these trials. The adjacent luminal gastrointestinal structures (small bowel and stomach) limit the dose delivered to the target; dose escalation using a novel technique results in better local control and overall survival.[11] In addition, CRT usually comprises 25 to 30 fractions and lasts 5 to 6 weeks; this leads to patient inconvenience and risk of treatment interruption and thus suboptimal control of micrometastasis. Thus, CRT is associated with unsatisfactory local control and significant toxicities.

Advances in radiotherapy enable more precise target delineation, treatment delivery, and dose escalation. Stereotactic body radiotherapy (SBRT) enables precise delivery of high-dose radiation to the target within a short period (typically ≤5 fractions). The American Society of Clinical Oncology guidelines suggest SBRT as a treatment option for LAPC patients who do not improve on systemic treatment or who are intolerant to chemotherapy.[12] This study reviews the technology, clinical application, and future direction of SBRT for treatment of pancreatic cancer.

STEREOTACTIC BODY RADIOTHERAPY

The use of a linear accelerator–based system (CyberKnife system; Accuray, Sunnyvale [CA], USA) and proton beam for SBRT of the pancreas has been reported.[13,14] SBRT of the pancreas is technically challenging; accurate target volume delineation, motion management, on-line imaging verification, radiation planning and delivery, and dose / fractionation are needed to ensure success.

Target Volume Delineation

To ensure accurate target volume delineation, fine-cut (1.5-2 mm), contrast-enhanced computed tomography (CT) in both arterial and venous phases is used to contour the tumour. The pancreatic tumour is best seen in the early venous phase as a hypodense lesion in contrast with the enhancing pancreatic parenchyma. The arterial phase shows whether there is coeliac and superior mesenteric artery invasion. Nonetheless, CT is prone to underestimate the size of the gross tumour volume.[15] Magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography also provide useful information.[16,17] Different imaging modalities (CT, positron emission tomography, diffusion-weighted MRI, and dynamic contrast-enhanced MRI) differ in target volume and gross tumour volume definitions.[17] Thus, further studies of the radiological and pathological correlation are required.

Motion Management

The magnitude of motion of the pancreatic tumour is highly variable and is estimated to be up to 2 to 3 cm in the craniocaudal direction.[18] Planning with four-dimensional CT may not be sufficient, as tumour motion in most patients exceeds the predicted range by >10%.[19] The use of the active breathing control technique can restrict the amplitude of pancreas movement to 2.5 mm.[20] Gated delivery for radiotherapy around the end exhale position (that is the most stable position in the breathing cycle) can also reduce the target volume amplitude.[21]

On-line Imaging Verification

SBRT of the pancreas must be performed under image guidance, as inter-fractionation movement can be substantial. A reliable daily on-line treatment verification system of tumour localisation is necessary. Treatment verification based on bony anatomies is insufficient.[22] Kilovoltage imaging and cone-beam CT are commonly used, but both have poor soft-tissue (including pancreatic tumour) resolution. Placement of fiducial markers under endoscopic guidance or via the percutaneous route is essential.[23] The fiducials act as a surrogate to allow targeting of the daily tumour position (by kilovoltage or cone-beam CT) and real-time tracking of tumour motion during radiotherapy delivery (Figure 1). Planning CT is usually performed 5 to 7 days after implantation of markers to minimise their migration. Insertion of a biliary stent is an alternative surrogate.

Radiation planning and delivery

The planning target volume usually includes a margin of 2 to 3 mm to account for the setup uncertainty. Occasionally, non-uniform margin expansion is allowed to spare the adjacent duodenum or stomach. Elective nodal irradiation is usually not recommended. The dose is prescribed to the periphery of the lesion to allow 90% to 95% coverage; dose heterogeneity sometimes exceeds 15% to 20%. SBRT can be delivered via intensity-modulated radiotherapy or volumetric-modulated arc therapy. A flattening filter-free mode with an increased dose rate is preferred in order to shorten the treatment time and minimise inter-fractionation movement of the tumour. Figure 2 shows the representative plan and dose-volume histogram of SBRT for pancreatic cancer.

Dose / Fractionation

The optimal dose / fractionation of SBRT of the

Figure 1. (a) Coronal, (b) axial, and (c) sagittal views of on-line cone-beam computed tomography for daily alignment using fiducials as surrogates.

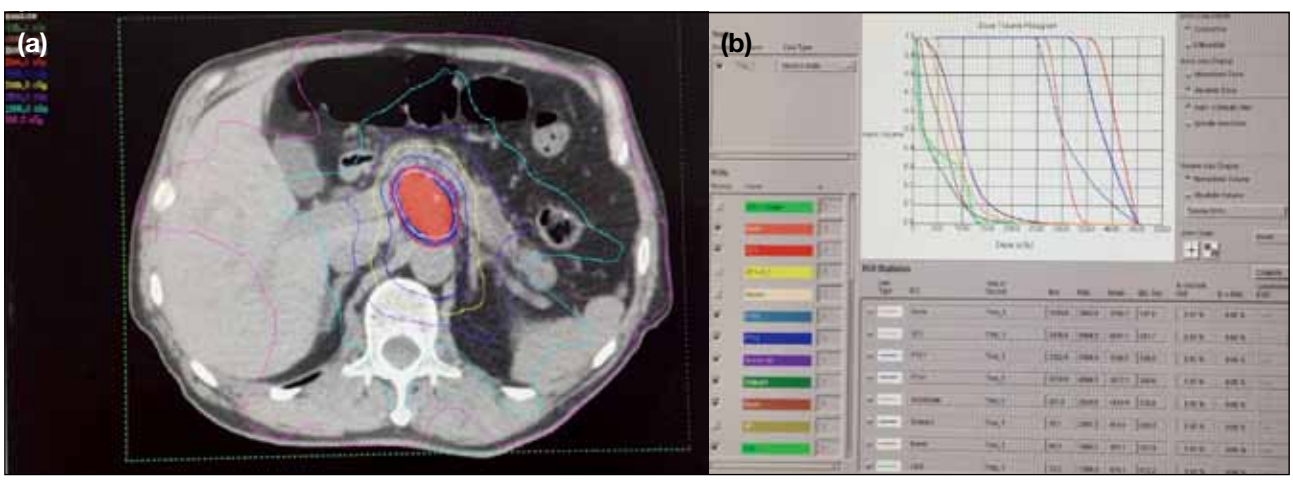

Figure 2. (a) Computed tomography depicts a treatment plan of 33 Gy in 5 fractions for a tumour in the head of the pancreas, and (b) the corresponding dose-volume histogram.

pancreas is not yet known. In a Stanford study of 167 patients treated with single or multiple fractionation, the two regimens were comparable for local control and overall survival, but multiple fractionation resulted in less grade 2 or above toxicities.[24] In a meta-analysis of 16 trials of SBRT for pancreatic cancer, the dose was converted to 2 Gy equivalent dose (EQD2) and biologically equivalent dose (BED).[25] Late toxicity was highly correlated with EQD2 (taking a/b = 3) and 5% of patients developed grade 2 or above toxicity and grade 3 or above toxicity at 65 Gy and 80 Gy, respectively.[25] Tumour control appeared to be less dose-dependent (taking a/b = 10); 75 Gy BED was highly effective and resulted in a local control rate of 75%, whereas >75 Gy BED did not prolong survival and was not safe.[25] Based on the currently available evidence, multiple fractionation is recommended, with toxicity estimated according to EQD2 / BED prescription dose and duodenal dose constraints. Table 1 summarises the commonly used regimens and their equivalent EQD2 of SBRT for pancreatic cancer.

Table 1. Common stereotactic body radiotherapy regimens for pancreatic cancer and 2 Gy equivalent dose (EQD2) values for prescription doses to the tumour (10 Gy) and recalculated prescription doses for the equivalent dose effect at the duodenum (3 Gy).

No. of fractions	Dose per fraction (Gy)	Total dose (Gy)	EQD2 (10 Gy)	EQD2 (3 Gy)
1	25	25	72.92	140.00
3	8	24	36.00	52.80
3	10	30	50.00	78.00
3	12	36	66.00	108.00
3	15	45	93.75	162.00
5	5	25	31.25	40.00
5	6	30	40	54
5	6.6	33	45.65	63.36
5	7	35	49.58	70.00
5	10	50	83.33	130.00
6	7.5	45	65.63	94.5

Clinical Outcome

Table 2 summarises selected trials of SBRT for LAPC.[26-35] In the Stanford phase I study of 15 LAPC patients treated with 25 Gy single fraction using the CyberKnife, the 1-year local control rate was 100%, but all patients later died of metastatic disease.[26] In the Stanford phase II study of a 25 Gy SBRT boost after concurrent CRT using 5-fluorouracil (45 Gy), the local control rate was 94%, but the median survival was only 8.3 months, with 69% and 12.5% of patients developing grade 1 or 2 toxicities and acute grade 3 or above toxicities, respectively.[27] In a study of combined chemotherapy with SBRT (one cycle of induction gemcitabine of 1000 mg/m^2 followed by SBRT of 25 Gy x 1 fraction followed by maintenance doses of gemcitabine), the 1-year local control rate was 94% to 100%, but 47% of patients developed late grade 2 or above toxicity and 5.6% of patients developed grade 4 duodenal perforation that required surgery.[28,36] These early studies of SBRT have shown good (90-100%) 1-year local control but substantial late gastrointestinal toxicity, which was postulated to be related to single fractionation. Therefore, subsequent trials have changed to multiple (3-5) fractionation.

Table 2. Selected studies of stereotactic body radiotherapy (SBRT) for locally advanced pancreatic cancer.

Study	Regimen	No. of patients	1-year local control (%)	Median overall survival (months)	Acute toxicity of grade 3 or above (%)	Late toxicity of grade 2 or above (%)	Chemotherapy
Koong et al,[26] 2004	25 Gy x 1	15	100	11	33	-	None
Koong et al,[27] 2005	25 Gy x 1 (boost)	16	94	8.3	12.5	-	External-beam radiotherapy with 5-fluorouracil before SBRT
Schellenberg et al,[28] 2008	25 Gy x 1	16	100	11.4	19	47	Gemcitabine before and after SBRT
Hoyer et al,[29] 2005	15 Gy x 3	22	57	5.4	79	94	None
Mahadevan et al,[30] 2010	8-12 Gy x 3	36	78	14.3	8	5.6	Gemcitabine after SBRT
Mahadevan et al,[31] 2011	8-12 Gy x 3	39	85	20.3	0	9	Gemcitabine x 2 before SBRT
Goyal et al,[32] 2012	20-25 Gy x 1 or 8-10 Gy x 3	19	65	14.4	16	11	68% received chemotherapy
Tozzi et al,[33] 2013	7.5 Gy x 6	30	86	11	20	0	Gemcitabine-based before SBRT
Gurka et al,[34] 2017	5-6 Gy x 5	38	82 (6 months)	12.2	5	7.9	Concurrent gemcitabine
Herman et al,[35] 2015	6.6 Gy x 5	49	78	13.9	2	10.6	SBRT followed by gemcitabine

Hypofractionated SBRT regimens (3-5 fractions) aim to reduce late gastrointestinal toxicity while maintaining local control. In a phase II trial of 22 LAPC patients treated with SBRT of 15 Gy x 3 fractions, the 1-year local control rate was 57% and the median survival was 5.4 months, and 79% and 4.5% of patients developed grade 2 toxicity and grade 4 toxicity, respectively.[29] The trial was criticised for inaccurate positioning, lack of dose constraint to the organ at risk, lack of fiducial placement, and exceptionally large planning target volume margin (a median of 136 ml vs. 41 ml in the Stanford study) that included both the primary and adjacent oedema. These probably account for the discrepancy of results from other similar trials. In a series of 36 LAPC patients who received 24-36 Gy in 3 fractions using a risk-adapted approach (based on the location of the tumour from the stomach and duodenum) followed by 6 months of chemotherapy with gemcitabine, the local control rate was 78% and the median survival was 14.3 months after a median follow-up of 24 months.[30] In this study, 25% and 8% of patients developed acute grade 2 toxicity and acute grade 3 toxicity, respectively, and 5.6% of patients developed late toxicity 3 months after SBRT.[30] In a subsequent study of 39 LAPC patients treated with SBRT using a similar adaptive approach after two cycles of chemotherapy, the local control rate was 85% and the median survival was 20.3 months after a median follow-up of 21 months.[31] Only 9% of patients developed late grade 3 toxicities such as bowel obstruction and gastrointestinal bleeding.[31] Studies of multi-fraction SBRT from Europe and the United States have also reported similar 1-year local control rates of 65% to 86%, median survival of 11-14 months, and an acceptable acute and late toxicity profile.[32-34] In a multicentre prospective phase II study using fiducial placement, image guidance verification, motion management, and planning under strict dose constraints, 49 LAPC patients received SBRT of 33 Gy in 5 fractions followed by gemcitabine, and the 1-year freedom from local progression rate was 78% and the median survival was 13.9 months.[35] Only 2% and 10.6% of patients developed acute and late grade 2 or above toxicities, respectively.[35] These studies of fractionated SBRT have reported local control rates of 65% to 86% (compared with 30% to 50% after CRT), with <10% of patients developing acute or late grade 3 or above gastrointestinal toxicity.

As Neoadjuvant Therapy

Borderline resectable pancreatic cancer (BRPC) has little chance of achieving R0 resection due to the abutment of the adjacent vascular structure. SBRT is justified as the neoadjuvant treatment for BRPC; the chance of margin-negative resection may increase if the area of vascular involvement is regressed or sterilised after treatment.

Table 3 summarises selected trials of SBRT for BRPC.[37-41] In a study of 57 BRPC patients treated with neo-adjuvant chemotherapy and SBRT using a dose-painting technique, the region of vascular involvement received a median of 35 Gy in 5 fractions and the remaining tumour received 25 Gy in 5 fractions.[37] In this study, 31 of 32 patients who underwent resection achieved an R0 resection; of whom three achieved a

Table 3. Selected studies of stereotactic body radiotherapy (SBRT) as neoadjuvant therapy for locally advanced pancreatic cancer (LAPC) or borderline resectable pancreatic cancer (BRPC).

Study	Regimen	No. of patients	Median overall survival (months)	Resection rate / R0 resection rate (%)	Complete response rate (%)	Acute toxicity of grade 3 or above (%)	Late toxicity of grade 2 or above (%)	Chemotherapy
Chuong et al,[37] 2013	6 Gy x 5	57 (BRPC), 16 (LAPC)	16.4 (BRPC), 15 (LAPC)	56.1 / 96.9 (BRPC)	9.3	0	5.3	Gemcitabine-based (94.6%), FOLFIRINOX (5.4%)
Mellon et al,[38] 2015	6 Gy x 5	110 (BRPC), 49 (LAPC)	19.2 (BRPC), 15 (LAPC)	51 / 96 (BRPC), 10 / 100 (LAPC)	7 (BRPC), 0 (LAPC)	0	-	Gemcitabine-based (82%), FOLFIRINOX (14%)
Rajagopalan et al,[39] 2013	12 Gy x 3 or 24 Gy x 1	7 (BRPC), 5 (LAPC)	47.2	100 / 91.7	25	33	-	Gemcitabine-based (92%)
Shaib et al,[40] 2016	12-15 Gy x 3	13 (BRPC)	11	61.5 / 100	0	0	0	Modified FOLFIRINOX (100%)
Hong et al,[41] 2014	5 GyE x 5	50 (resectable)	17	78 / 84	0	4.1	-	Concurrent capecitabine

complete pathological response and two achieved a near-complete pathological response (<10% viable cells).[37] The median OS was 16.4 months; no patient had acute grade 3 or above toxicity and 5.3% of patients developed late grade 3 or above toxicity.[37] In a subsequent study of 110 BRPC patients by the same group, 51% were able to undergo resection and 96% of them achieved R0 resection; the median OS was 34.2 months among surgically resected patients.[38] In a study of 12 BRPC patients who received neoadjuvant chemotherapy and SBRT, 92% of patients achieved R0 resection, 25% of patients achieved pathological complete response, and 16.7% of patients had <10% viable tumour cells.[39] In a phase I trial of 13 BRPC patients who received dose-escalating SBRT in 3 fractions to the planning target volume with a simultaneous in-field boost to the posterior margin after four cycles of modified FOLFIRINOX, no patient developed dose-limiting toxicity up to the level of 45 Gy in 3 fractions, and 62% of patients underwent resection and all achieved R0 resection.[40]

In the Harvard phase I study of 15 patients with resectable pancreatic cancer using proton therapy with dose-escalating hypofractionated treatment with concurrent capecitabine in a preoperative setting, no patient developed dose-limiting toxicity at a final level of 25 Gy in 5 fractions.[14] This led to a phase II study of 35 patients who received 25 Gy in 5 fractions in a neoadjuvant setting, and 4.1% of patients developed acute grade 3 toxicity.[41] Among the 50 patients in both studies, 39 underwent resection and 31 of them achieved R0 resection without 30-day mortality or anastomotic leak; the median survival was 27 months and 16% of patients with surgical resection had a locoregional recurrence.[41]

Overall, early results of SBRT in a neoadjuvant setting are promising. In BRPC patients who are able to undergo resection after neoadjuvant treatment, the OS is comparable with those with an upfront resectable disease.

As Adjuvant Therapy

In patients with resected pancreatic cancer, the local recurrence rate is high (20-60%). Adjuvant therapy is justified to reduce the risk of local recurrence and its related complications. In a study of 12 patients who underwent a margin-positive resection, the rate of freedom from local progression at 1 year was 70.7% and the 1-year OS was 81.8%.[42] The same group later reported 24 patients who underwent resection with close or positive margins followed by SBRT, the rate of freedom from local progression at 1 year was 66% and the 1-year OS was 80.4%, with a median OS of 26.7 months.[43] No patients developed acute grade 3 or above toxicity.[43] SBRT has the merit of short treatment duration that enables early integration of systemic chemotherapy.

As Re-irradiation for Local Recurrence

Most patients with local recurrence of pancreatic cancer after resection and CRT are not eligible for re-resection. SBRT may be a viable option for these patients. In a retrospective review of 18 patients who had local recurrence or progressive disease after CRT (in a median dose of 50.4 Gy in 28 fractions) and subsequently underwent SBRT (in a median dose of 25 [range, 20-27] Gy in 5 fractions), the median survival after SBRT was 8.8 (95% confidence interval, 1.2-16.4) months, and the rate of freedom from local progression at 6 and 12 months after SBRT was 78% and 62%, respectively.[44] In this study, 57% of patients achieved effective symptom palliation; no patient developed acute grade 3 or above toxicity, and one patient developed late grade 3 toxicity.[44] In a study of SBRT in 28 previously irradiated patients with a median follow-up of 5.9 months, the rate of freedom from local progression was 86%, and two patients developed late grade 3 gastrointestinal toxicities.[45]

For Elderly Patients

Pancreatic cancer is more common in older people, and its incidence peaks in those aged >80 years. According to the 2015 Hong Kong Cancer Registry, the incidence was 50.7 and 45.6 per 100,000 people aged 80 to 84 years and ≥85 years, respectively, compared with 11.6 per 100,000 people aged 45 to 65 years.[1] Elderly people often have poor performance status or multiple comorbidities that preclude them from surgical resection, systemic chemotherapy, or concurrent CRT. SBRT may be a viable option for them.

In a study of 26 patients aged ≥80 years and unsuitable for surgical resection who underwent SBRT (mostly 24 Gy in 1 fraction or 30-36 Gy in 3 fractions), the median OS and local control was 7.6 months and 11.5 months, respectively, with symptomatic improvement in pain, anorexia, and nausea and no acute or late grade 3 or above toxicities.[46] In a study of 20 patients with a median age of 83.2 years and a median Adult Comorbidity Evaluation-27 Index of 3, most were

treated with SBRT in 30-35 Gy in 5 fractions, and the median OS and recurrence-free survival rates were 6.4 months and 6.8 months, respectively.[47] In this study, 10 patients had no toxicities, whereas 7 and 3 patients had grade 1 or 2 and grade 3 or above toxicities, respectively.[47] SBRT is a safe and effective treatment option for elderly patients in whom surgical resection or chemotherapy is unsuitable.

Future Direction

SBRT is superior to conventional CRT for local control of pancreatic cancer. The acute toxicity profile is mild, and most side-effects are grade 1 to 2. Late grade 3 or above complications are uncommon (<10%) after multi-fraction regimens. It is a viable option for LAPC and BRPC in adjuvant and recurrent settings. Nonetheless, whether the benefit of local control can translate to survival is not known. In the LAP07 trial, the addition of CRT only improved local control but not OS. This may be partly due to a high rate of distant metastasis. Recent advancements in systemic chemotherapy with FOLFIRINOX and gemcitabine / nab-paclitaxel have improved survival in patients with metastatic disease and in LAPC patients.[48,49] SBRT has the merit of delivering a high dose in a short period (typically within 5 days) for local control, enabling minimal disruption of systemic chemotherapy to achieve better distant control. The best OS occurs in patients with chemotherapy well integrated into pre- and post-SBRT.[25] Therefore, how to integrate SBRT with multi-agent systemic chemotherapy is an important research focus.

To date, there is no prospective randomised trial of SBRT to guide clinical practice. The Stanford group is conducting a phase III trial to compare modified FOLFIRINOX with or without SBRT in LAPC patients (NCT01926197). The Alliance group is preparing a phase II trial (A021501) to compare FOLFIRINOX with or without SBRT in BRPC patients. Multi-fraction SBRT has shown the benefit of dose escalation and a tolerable toxicity profile. Further SBRT dose-escalation trials are ongoing (Table 4). These trials aim to address the best sequence of combining SBRT with chemotherapy and the optimal dose of SBRT.

Identifying biomarkers also helps select patients who will most benefit from SBRT. An autopsy study has shown that intact SMAD4 protein correlates with local disease progression, whereas the loss of SMAD4 protein more commonly correlates with distant progression.[5] The SMAD4 protein may serve as a potential biomarker for identifying most suitable patients for SBRT. A combination of systemic chemotherapy with SBRT enables more patients to undergo surgical resection; therefore new imaging, liquid and tissue biomarkers are needed to evaluate responses along the course of treatment, to determine who is most likely to benefit from an aggressive surgical approach.

Reducing tumour hypoxia with drugs optimises the therapeutic ratio of SBRT, as there is less opportunity for tumour re-oxygenation in the hypo-fractionation regimen and it may render cancer cells more radio-resistant. Nelfinavir (NCT01959672) and metformin (NCT02153450) are being investigated in combination with SBRT of the pancreas. Although results of immunotherapy in pancreatic cancer are disappointing so far, multiple studies are underway in combining SBRT with novel systemic therapy and immunotherapy.

Advancement of radiation technology (such as cone-beam CT verification, fiducial marker tracking, respiratory motion management) has improved the precision of radiation delivery to the pancreas. Nonetheless, the dynamic nature of the duodenum and stomach resulting in day-to-day variation that accounts

Table 4. Selected trials evaluating the optimal dose of stereotactic body radiotherapy (SBRT) or a combination of multi-agent chemotherapy and SBRT for locally advanced pancreatic cancer (LAPC) or borderline resectable pancreatic cancer (BRPC).

Trial	Patient Population	Design	Regimen	Chemotherapy
NCT02873598	LAPC	Phase I	9-11 Gy x 3	Induction FOLFIRINOX
NCT02643498	LAPC	Phase I	9-11 Gy x 3	Induction FOLFIRINOX
NCT02454140	LAPC / BRPC	Phase I	8-12 Gy x 5	Not mentioned
NCT01926197 (PanCRS trial)	LAPC	Phase III	8 Gy x 5	Modified FOLFIRINOX +/- SBRT
NCT01992705 (GCC1324)	BRPC	Phase I	6 Gy x 5	Induction FOLFIRINOX
NCT02128100 (BCC-RAD-13)	LAPC	Phase II	6.5 Gy x 5	Induction FOLFIRINOX

for substantial inter-fractionation errors. Strategies to further minimise small bowel toxicity are needed. Adaptive radiotherapy involves altered radiation delivery based on adaptive re-planning using daily cone-beam CT images. Adaptive re-planning has been reported to reduce the dose to the adjacent duodenum and improve the dose homogeneity to the target.[50]

CONCLUSION

SBRT of the pancreas is safe and effective. Target delineation, motion management, and on-line image guidance are crucial for treatment delivery. Clinical indications for SBRT remain to be established. Future studies should focus on combining systemic therapy with surgery, utilising novel biomarkers to select patients, testing with radiation sensitisers or immunotherapy, and further enhancing the treatment accuracy by adaptive strategies. Further randomised studies are needed to compare with the current standard to define its clinical application.

REFERENCES

1. The Hong Kong Cancer Registry. Available from: http://www3.ha.org.hk/cancereg/statistics.html. Accessed 19 Feb 2017.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012;62:10-29. cross ref
3. Katz MH, Wang H, Fleming JB, Sun CC, Hwang RF, Wolff RA, et al. Long-term survival after multidisciplinary management of resected pancreatic adenocarcinoma. Ann Surg Oncol. 2009;16:836-47. cross ref
4. Griffin JF, Smalley SR, Jewell W, Paradelo JC, Reymond RD, Hassanein RE, et al. Patterns of failure after curative resection of pancreatic carcinoma. Cancer. 1990;66:56-61. cross ref
5. Iacobuzio-Donahue CA, Fu B, Yachida S, Luo M, Abe H, Henderson CM, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. J Clin Oncol. 2009;27:1806-13. cross ref
6. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Gastrointestinal Tumor Study Group. Cancer. 1987;59:2006-10. cross ref
7. Loehrer PJ Sr, Feng Y, Cardenes H, Wagner L, Brell JM, Cella D, 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;29:4105-12. cross ref
8. Huguet F, André T, Hammel P, Artru P, Balosso J, Selle F, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. J Clin Oncol. 2007;25:326-31. cross ref
9. Chauffert B, Mornex F, Bonnetain F, Rougier P, Mariette C, Bouche O, 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;19:1592-9. cross ref
10. Hammel P, Huguet F, van Laethem JL, Goldstein D, Glimelius B, Artru P, 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;315:1844-53. cross ref
11. Ben-Josef E, Schipper M, Francis IR, Hadley S, Ten-Haken R, Lawrence T, et al. A phase I/II trial of intensity modulated radiation (IMRT) dose escalation with concurrent fixed-dose rate gemcitabine (FDR-G) in patients with unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys. 2012;84:1166-71. cross ref
12. Balaban EP, Mangu PB, Khorana AA, Shah MA, Mukherjee S, Crane CH, et al. Locally advanced, unresectable pancreatic cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2016;34:2654-68. cross ref
13. Berber B, Sanabria JR, Braun K, Yao M, Ellis RJ, Kunos CA, et al. Emerging role of stereotactic body radiotherapy in the treatment of pancreatic cancer. Expert Rev Anticancer Ther. 2013;13:481-7. cross ref
14. Hong TS, Ryan DP, Blaszkowsky LS, Mamon HJ, Kwak EL, Mino-Kenudson M, et al. Phase I study of preoperative short-course chemoradiation with proton beam therapy and capecitabine for resectable pancreatic ductal adenocarcinoma of the head. Int J Radiat Oncol Biol Phys. 2011;79:151-7. cross ref
15. Arvold ND, Niemierko A, Mamon HJ, Fernandez-del Castillo C, Hong TS. Pancreatic cancer tumor size on CT scan versus pathologic specimen: implications for radiation treatment planning. Int J Radiat Oncol Biol Phys. 2011;80:1383-90. cross ref
16. Hall WA, Mikell JL, Mittal P, Colbert L, Prabhu RS, Kooby DA, et al. Tumor size on abdominal MRI versus pathologic specimen in resected pancreatic adenocarcinoma: implications for radiation treatment planning. Int J Radiat Oncol Biol Phys. 2013;86:102-7. cross ref
17. Dalah E, Moraru I, Paulson E, Erickson B, Li XA. Variability of target and normal structure delineation using multimodality imaging for radiation therapy of pancreatic cancer. Int J Radiat Oncol Biol Phys. 2014;89:633-40. cross ref
18. Bussels B, Goethals L, Feron M, Bielen D, Dymarkowski S, Suetens P, et al. Respiration-induced movement of the upper abdominal organs: a pitfall for the three-dimensional conformal radiation treatment of pancreatic cancer. Radiother Oncol. 2003;68:69-74. cross ref
19. Minn AY, Schellenberg D, Maxim P, Suh Y, McKenna S, Cox B, et al. Pancreatic tumor motion on a single planning 4D-CT does not correlate with intrafraction tumor motion during treatment. Am J Clin Oncol. 2009;32:364-8. cross ref
20. Langen KM, Jones DT. Organ motion and its management. Int J Radiat Oncol Biol Phys. 2001;50:265-78. cross ref
21. Heerkens HD, van Vulpen M, van den Berg CA, Tijssen RH, Crijns SP, Molenaar IQ, et al. MRI-based tumor motion characterization and gating schemes for radiation therapy of pancreatic cancer. Radiother Oncol. 2014;111:252-7. cross ref
22. Yang W, Fraass BA, Reznik R, Nissen N, Lo S, Jamil LH, et al. Adequacy of inhale/exhale breathhold CT based ITV margins and image-guided registration for free-breathing pancreas and liver SBRT. Radiat Oncol. 2014;9:11. cross ref
23. Jayachandran P, Minn AY, Van Dam J, Norton JA, Koong AC, Chang DT, et al. Interfractional uncertainty in the treatment of pancreatic cancer with radiation. Int J Radiat Oncol Biol Phys. 2010;76:603-7. cross ref
24. Pollom EL, Alagappan M, von Eyben R, Kunz PL, Fisher GA, Ford JA, et al. Single- versus multifraction stereotactic body radiation therapy for pancreatic adenocarcinoma: outcomes and toxicity. Int J Radiat Oncol Biol Phys. 2014;90:918-25. cross ref

25. Brunner TB, Nestle U, Grosu AL, Partridge M. SBRT in pancreatic cancer: what is the therapeutic window? Radiother Oncol. 2015;114:109-16. cross ref
26. Koong AC, Le QT, Ho A, Fong B, Fisher G, Cho C, et al. Phase I study of stereotactic radiosurgery in patients with locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2004;58:1017-21. cross ref
27. Koong AC, Christofferson E, Le QT, Goodman KA, Ho A, Kuo T, et al. Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2005;63:320-3. cross ref
28. Schellenberg D, Goodman KA, Lee F, Chang S, Kuo T, Ford JM, et al. Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2008;72:678-86. cross ref
29. Hoyer M, Roed H, Sengelov L, Traberg A, Ohlhuis L, Pedersen J, et al. Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. Radiother Oncol. 2005;76:48-53. cross ref
30. Mahadevan A, Jain S, Goldstein M, Miksad R, Pleskow D, Sawhney M, et al. Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2010;78:735-42. cross ref
31. Mahadevan A, Miksad R, Goldstein M, Sullivan R, Bullock A, Buchbinder E, et al. Induction gemcitabine and stereotactic body radiotherapy for locally advanced nonmetastatic pancreas cancer. Int J Radiat Oncol Biol Phys. 2011;81:e615-22. cross ref
32. Goyal K, Einstein D, Ibarra RA, Yao M, Kunos C, Ellis R, et al. Stereotactic body radiation therapy for nonresectable tumors of the pancreas. J Surg Res. 2012;174:319-25. cross ref
33. Tozzi A, Comito T, Alongi F, Navarria P, Iftode C, Mancosu P, et al. SBRT in unresectable advanced pancreatic cancer: preliminary results of a mono-institutional experience. Radiat Oncol. 2013;8:148. cross ref
34. Gurka MK, Kim C, He AR, Charabaty A, Haddad N, Turocy J, et al. Stereotactic body radiation therapy (SBRT) combined with chemotherapy for unresected pancreatic adenocarcinoma. Am J Clin Oncol. 2017;40:152-7. cross ref
35. Herman JM, Chang DT, Goodman KA, Dholakia AS, Raman SP, Hacker-Prietz A, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. Cancer. 2015;121:1128-37. cross ref
36. Schellenberg D, Kim J, Christman-Skieller C, Chun CL, Columbo LA, Ford JM, et al. Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2011;81:181-8. cross ref
37. Chuong MD, Springett GM, Freilich JM, Park CK, Weber JM, Mellon EA, et al. Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. Int J Radiat Oncol Biol Phys. 2013;86:516-22. cross ref
38. Mellon EA, Hoffe SE, Springett GM, Frakes JM, Strom TJ, Hodul PJ, et al. Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma. Acta Oncol. 2015;54:979-85. cross ref
39. Rajagopalan MS, Heron DE, Wegner RE, Zeh HJ, Bahary N, Krasinskas AM, et al. Pathologic response with neoadjuvant chemotherapy and stereotactic body radiotherapy for borderline resectable and locally-advanced pancreatic cancer. Radiat Oncol. 2013;8:254. cross ref
40. Shaib WL, Hawk N, Cassidy RJ, Chen Z, Zhang C, Brutcher E, et al. A phase 1 study of stereotactic body radiation therapy dose escalation for borderline resectable pancreatic cancer after modified FOLFIRINOX (NCT01446458). Int J Radiat Oncol Biol Phys. 2016;96:296-303. cross ref
41. Hong TS, Ryan DP, Borger DR, Blaszkowsky LS, Yeap BY, Ancukiewicz M, et al. A phase 1/2 and biomarker study of preoperative short course chemoradiation with proton beam therapy and capecitabine followed by early surgery for resectable pancreatic ductal adenocarcinoma. Int J Radiat Oncol Biol Phys. 2014;89:830-8. cross ref
42. Rwigema JC, Parikh SD, Heron DE, Howell M, Zeh H, Moser AJ, et al. Stereotactic body radiotherapy in the treatment of advanced adenocarcinoma of the pancreas. Am J Clin Oncol. 2011;34:63-9. cross ref
43. Rwigema JC, Heron DE, Parikh SD, Zeh HJ 3rd, Moser JA, Bahary N, et al. Adjuvant stereotactic body radiotherapy for resected pancreatic adenocarcinoma with close or positive margins. J Gastrointest Cancer. 2012;43:70-6. cross ref
44. Wild AT, Hiniker SM, Chang DT, Tran PT, Khashab MA, Limaye MR, et al. Re-irradiation with stereotactic body radiation therapy as a novel treatment option for isolated local recurrence of pancreatic cancer after multimodality therapy: experience from two institutions. J Gastrointest Oncol. 2013;4:343-51.
45. Lominska CE, Unger K, Nasr NM, Haddad N, Gagnon G. Stereotactic body radiation therapy for reirradiation of localized adenocarcinoma of the pancreas. Radiat Oncol. 2012;7:74. cross ref
46. Kim CH, Ling DC, Wegner RE, Flickinger JC, Heron DE, Zeh H, et al. Stereotactic body radiotherapy in the treatment of pancreatic adenocarcinoma in elderly patients. Radiat Oncol. 2013;8:240. cross ref
47. Yechieli RL, Robbins JR, Mahan M, Siddiqui F, Ajlouni M. Stereotactic body radiotherapy for elderly patients with medically inoperable pancreatic cancer. Am J Clin Oncol. 2017;40:22-6. cross ref
48. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364:1817-25. cross ref
49. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369:1691-703. cross ref
50. Li Y, Hoisak JD, Li N, Jiang C, Tian Z, Gautier Q, et al. Dosimetric benefit of adaptive re-planning in pancreatic cancer stereotactic body radiotherapy. Med Dosim. 2015;40:318-24. cross ref