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Review

Hepatobiliary

Stereotactic radiotherapy of pancreatic cancer: techniques and results

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Abstract

Introduction

Stereotactic body radiotherapy in the treatment of pancreatic carcinoma is a recent technique. The aim of this analysis is to present a summary of techniques and clinical results.

Material and Methods

Stereotactic body radiotherapy allows to perform a local treatment of the tumour in shortened time (1–5 days) compared with traditional treatments (about 1 month) but requires complex planning and delivery techniques with specific accessories for image-guided radiotherapy. The studies published to date are characterised by small series and very different methods in terms of dose, fractionation, techniques and evaluation modalities.

Results

The preliminary published results are positive in terms of tumour response (ORR: 50%) and local control of the tumour (crude rate: 80%). However, gastrointestinal toxicity seems to be the main limitation of stereotactic body radiotherapy, especially at the duodenal level.

Conclusion

If stereotactic body radiotherapy of pancreatic carcinoma will be standardised and optimised, reducing the risk of bowel toxicity, in the future it may have an increasing role in the field of integrated treatments of this tumour.

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Introduction

The prognosis of pancreatic cancer pancreas is very unfavourable. Even in patients with non-metastatic disease at diagnosis, recurrences after primary therapy are very common both as a local relapse/progression and as distant metastases. Local recurrence rate, even of patients operated on, reached percentages of 70%–80%[1,2]. In addition, local disease progression produces severe symptoms (pain, biliary and/or intestinal obstruction, malnutrition) capable of significantly worsening the patients' quality of life.

Radiotherapy (RT) was used to promote local control of the disease. RT, usually associated with concurrent and adjuvant chemotherapy, is potentially useful to improve the resection rate[3] and control symptoms in locally advanced carcinomas[4] and to reduce the risk of recurrence in resected patients[5]. The main limitation of RT is the presence of radiosensitive organs in the upper abdomen in close proximity with the pancreas. In fact, due to these anatomic relationships, RT can produce severe side effects especially at the level of the duodenum. Therefore, a strong interest in the use of innovative precision RT techniques has developed, with the aim to administer effective doses

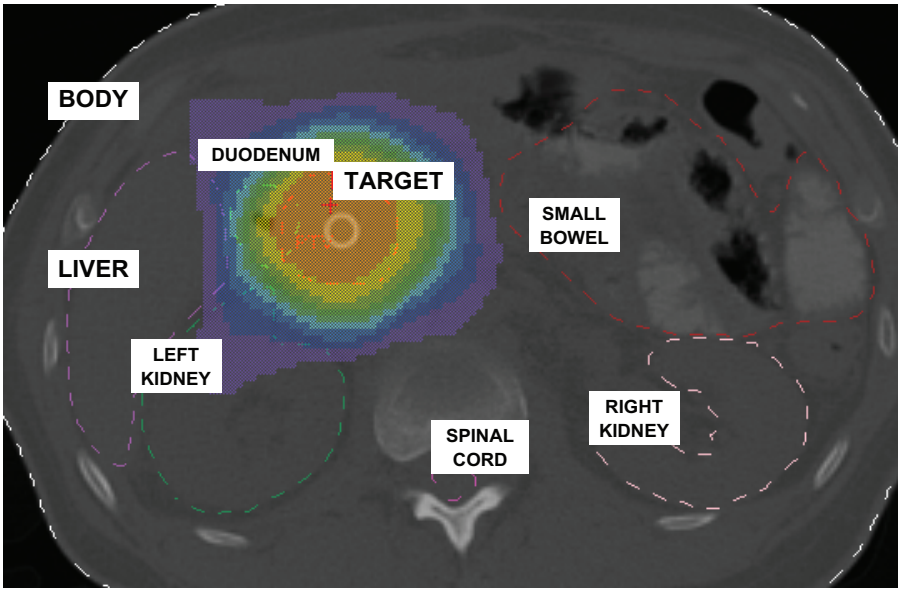

Figure 1: Dose distribution in a pancreatic head carcinoma with SBRT; there is a clear concentration of the dose on the target with healthy organ sparing. SBRT, stereotactic body radiotherapy.

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to the target while reducing the irradiation of healthy organs.

One of the most promising newer techniques is stereotactic body radiotherapy (SBRT). The American Society of Radiation Oncology defines SBRT as external beam RT used to deliver a high dose of radiation very precisely to an extracranial target within the body, as a single dose or a small number of fractions[6]. In addition, by improving the accuracy of treatment delivery, thus reducing the amount of normal tissue irradiated (Figure 1), the high radiation dose per treatment (fraction) can potentially ablate all tissue in the treated area.

Due to these characteristics, SBRT is able to deposit high amounts of dose to the target, limiting damage to the surrounding healthy tissue. However, in literature, there is currently only limited evidence, represented by preliminary studies generally performed on small patient populations[7–22,]. Therefore, the purpose of this analysis is to present a summary of techniques and clinical results of SBRT in pancreatic cancer.

Materials and Methods

All clinical experience with the SBRT of pancreatic tumours has been published over the past 10 years. In most cases, they were phase 1–2 trials[9–11,13,21], case series[8,16,19,22] or retrospective studies[7,12,14–18] involving small patient populations with short observation time. In most cases, SBRT was used in the treatment of patients with locally advanced cancer[7–11,13–16,18–22] and in some others even for metastatic patients[7,8,18].

SBRT allows the administration of high doses on precisely defined targets. However, several studies used different methods of detection and localisation of macroscopic tumour using diagnostic-quality CT scan[9–11,13,14,16,17,22] or 18-FDG-PET scan[21] or both[7,19,20]. Furthermore, different systems to precisely define the organ mo-tion due to respiratory movements were widely used. For this purpose, planning techniques based on 4D-CT[17,18], cine-mode CT systems plus active breathing control[13] (Figure 2) or restricted gated respiratory motion[21] have been used. In addition, in most studies radiopaque fiducials were implanted in the tumour to facilitate the visualisation of target position before each treatment[7,8,10–12,14,15,16–22].

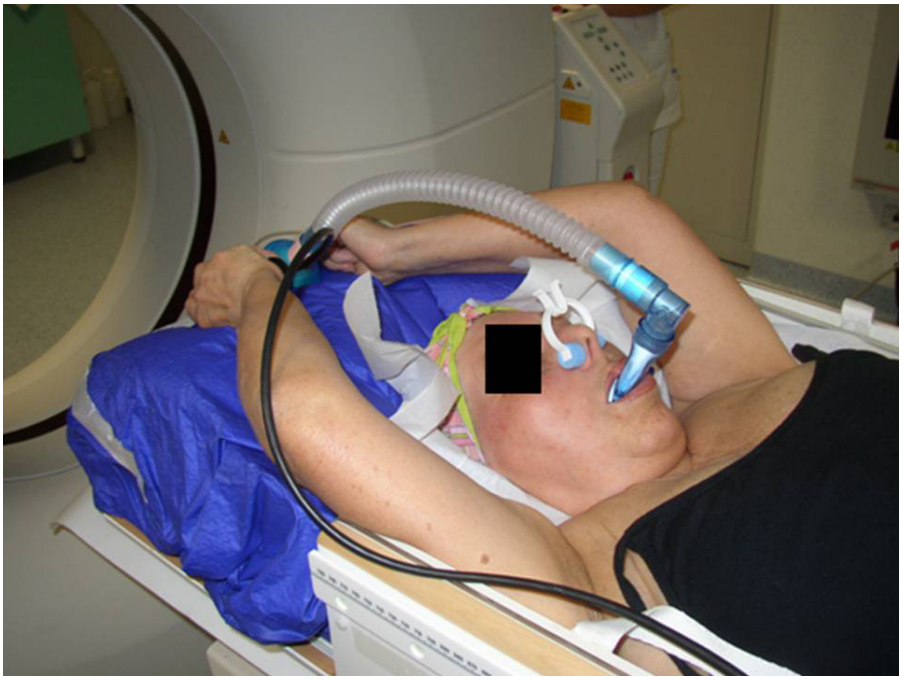

Figure 2: Use of the active breathing control (ABC) to reduce the organ motion during an SBRT treatment. SBRT, stereotactic body radiotherapy.

In certain studies, a margin was added between macroscopic tumour (gross tumour volume: GTV) and the so-called clinical target (clinical target volume: CTV) to consider the possible presence of microscopic disease around the visible disease. Even an additional margin between CTV and overall target (planning target volume: PTV) was added to account for organ motion and set-up errors. These margins were typically less than or equal to 5 mm[8,12,15,18–22].

In most studies, the CyberKnife system (robotic treatment machine for high-precision image-guided RT) was used[7,8,10–12,14,15,16–19,21,22], while in some studies intensity-modulated RT[20] (Figure 3), 3D technique with non-coplanar beams[13] (Figure 4) or standard 3D technique[9] were used.

In some studies, variable dose levels were used in different patients[7,8,11,13–15,16–18,21,22], and only few series used a single dose level[9,10,16,19,20]. Even dose prescription and reporting were variable between the different studies. Moreover, both treatments with the dose delivered in a single fraction (so-called radiosurgery)[11,17–20] and treatments with fractionated dose[7,9,12–15,16,22] were used. In some studies, SBRT was used as a boost after a standard RT treatment[10,12,21], and in most studies, SBRT treatment was integrated with chemotherapy given before[11,13,21] or after SBRT[7,14,17] or both[15,18–20].

Results

In the studies reporting tumour response evaluation, the rate of complete response was 0–30%[7,8,13,16,22] and the overall response rate was 9–69% (median: 50%)[7–9,13,16,21,22]. In studies reporting median survival in patients with locally advanced disease, this was 5.7–24 months (median: 11.6 months)

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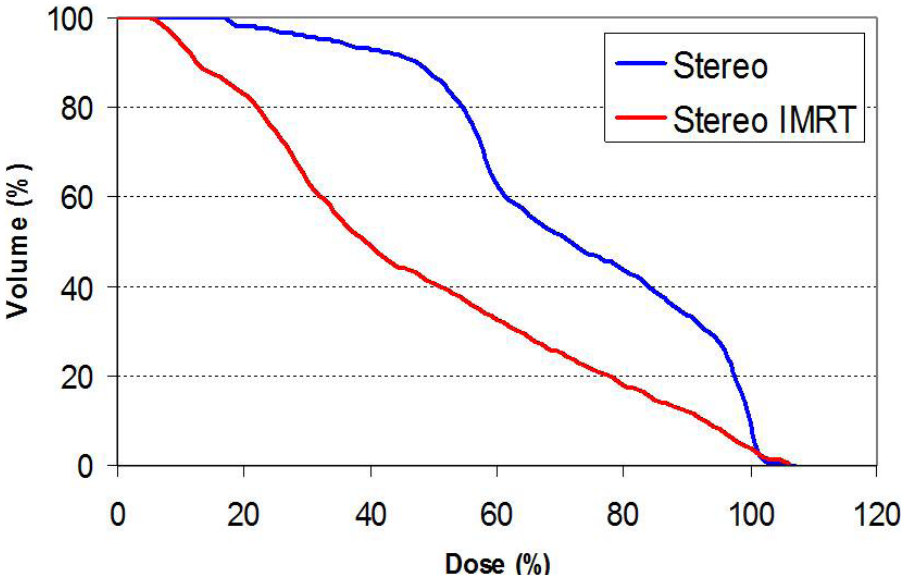

Figure 3: Dose–volume histogram on duodenal irradiation in an SBRT treatment of a pancreatic head carcinoma; the two curves refer to a standard (3D conformal) treatment and a modulated (IMRT) treatment. The net reduction allowed by the use of IMRT is clearly evident. SBRT, stereotactic body radiotherapy, IMRT, intensity-modulated radiation therapy.

with a 1-year survival between 5% and 60% (median 41%)[7,8,9–15,16–21] (Table 1). In studies on patients with unresected tumour, local control of disease was achieved in 56–94% of cases (median: 82%)[7,9,10,13–15,16,20,21]. Some studies even reported 1-year local progression-free survival, which was of 38–94% (median 68%)[8,17,18,20,21].

In four studies, no patient showed grade >3 toxicity[11,16,17,22]. Gastric or intestinal perforation was reported in four studies[9,16,19,20]. Other studies reported patients showing gastrointestinal ulceration, bleeding, stenosis or obstruction[7,8,13–15,21]. Of the four studies reporting gastrointestinal perforation, two had used a single dose of 25 Gy[19,20] and one study had used a total dose of 45 Gy in three fractions of 15 Gy[9]. Only one study reported a case of fatal toxicity due to complications from severe vomiting[18].

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

The studies on SBRT of pancreatic carcinoma published to date did not compare different methods of treatment and enrolled only a small number of patients. Therefore, it is difficult to compare the results obtained by SBRT with other treatment techniques. In addition, some studies even enrolled patients with metastatic disease, which should be considered in evaluating the results in terms of survival.

Another issue about the available studies on SBRT is the short follow-up (median: 8 months). Even this short follow-up should be considered

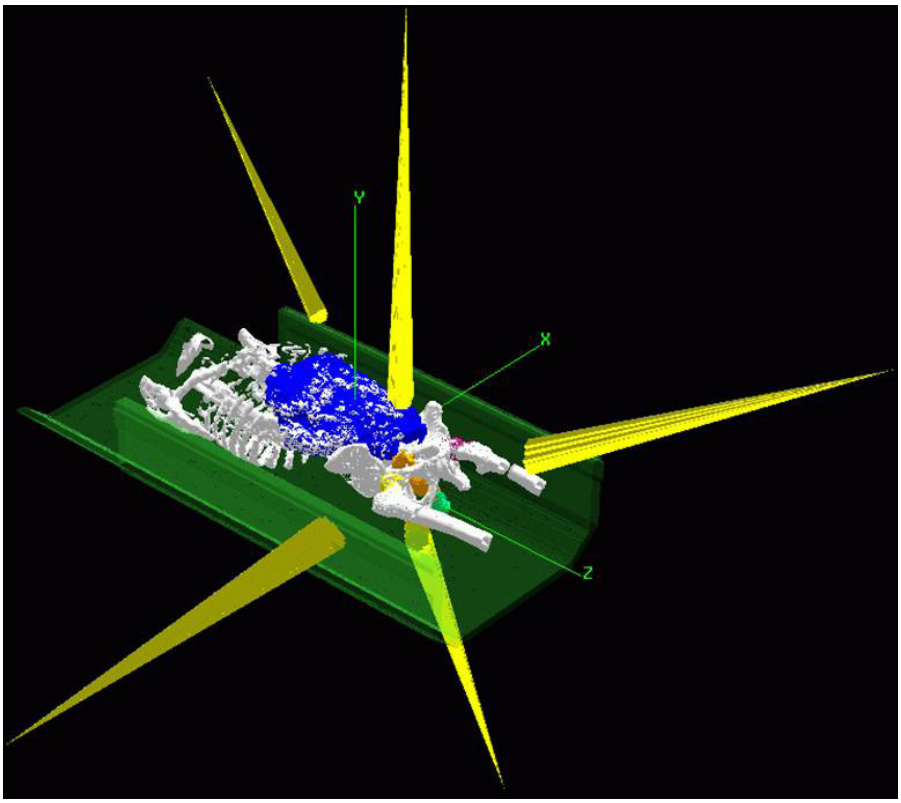

Figure 4: Spatial position of non-coplanar beams in an SBRT treatment. SBRT, stereotactic body radiotherapy.

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Table 1 Results of studies on stereotactic radiotherapy and radiosurgery in pancreatic carcinoma

Author (year)	Study design	Patients	Treatment technique	Overall survival median, months(1 year, %)	Grade ≥ 3 toxicity (%)
Koong (2004)	Phase I	15	CyberKnife	11	0
Koong (2005)	Phase II	16	CyberKnife	7.7 (15)	Acute gastroparesis: 10.5
Hoyer (2005)	Phase III	22	Standard LINAC-MLC	5.7 (5)	Gastric-duodenal Mucositis/ulceration: 18.1, Gastric perforation: 4.5
Schellenberg (2008)	Case series	16	CyberKnife	11.4 (50)	Gastric ulcer: 6.2, Duodenal stenosis: 6.2, Duodenal perforation: 6.2
Seo (2009)	Phase I	30	CyberKnife	14 (60)	Duodenal obstruction: 3.3
Didolkar (2010)	Retrospective	85	CyberKnife	8.6	Duodenitis: 14.1, Gastritis: 12.9, Diarrhoea: 3.5, Duodenal haemorrhage or Obstruction: 8.2
Shen (2010)	Case series	20	CyberKnife	NR	0
Mahadevan (2010)	Retrospective	36	CyberKnife	14.3	Vomiting: 5.5, Vena cava thrombosis: 2.7, Gastrointestinal bleeding: 5.5
Polistina (2010)	Case series	23	CyberKnife	10.6 (39.1)	0%
Rwigema (2011)	Retrospective	71	CyberKnife or Trilogy-IMST	10.3 (41)	Nausea: 1.4, Pain: 1.4, Gastroparesis: 1.4
Schellenberg (2011)	Case series	20	IMRT	11.8 (50)	Duodenal perforation: 5
Mahadevan (2011)	Retrospective	39	CyberKnife	20	Gastroduodenal bleeding/ obstruction: 9
Goyal (2012)	Case series	19	CyberKnife	14.4 (56)	Gastrointestinal ulcer: 16
Macchia (2012)	Phase I	16	Standard LINAC-MLC	24	Duodenal bleeding: 6.2
Lominska (2012)	Retrospective	28	CyberKnife	5.9 (18)	Bowel obstruction: 3.6, Gastric perforation: 3.6
Rwigema (2012)	Retrospective	24	CyberKnife or Trilogy-IMST	26.7 (80.4)	0

LINAC, linear accelerator; IMRT, intensity-modulated radiation therapy, MLC, multileaf collimator; IMST, intensity-modulated stereotactic therapy.

in evaluating the results and particularly the high local control rates reported in most studies. In fact, at least in part, these high rates may arise from the short observation time of patients.

The wide variability of simulation techniques, of GTV delineation modalities and also of GTV to CTV margins and of CTV to PTV margins, should equally be noted. The comparison between dose and clinical results is not simple due to the variable doses and variable number of fractions used within the same studies. Even the impact of chemotherapy treatment is hardly analysable since in six studies only some patients received this treatment[8,11,13,17,18,21]. As for the dose–effect relationship, evaluation is equally complicated by the use of very different prescription methods between different studies.

Tumour response to SBRT was highly variable in the different studies with an overall response rate ranging between 9% and 69%. This high variability may depend on the different doses, the different imaging methods and even the different scales used for response evaluation. However, considering the median value of clinical response in all the studies (ORR: 50%), this looks positive when compared with the results of fractionated chemoradiation of pancreatic cancers (ORR: 0–36%)[3].

The overall survival seems quite encouraging since these values were

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generally close to 1 year (median value: 11.6 months) therefore quite similar compared with that recorded in a series of patients undergoing standard chemoradiation (8.6–13.0 months)[3]. Even the results in terms of local control were positive with the majority of studies reporting values between 80% and 86%[11,13,15,16,19]. However, it should be highlighted again that the low recurrence rate could arise from the short observation time.

The results in terms of toxicity confirmed that even with this technique, the greater risk of toxicity concerns the gastrointestinal tract. Gastric or intestinal perforations were observed in four studies[9,16,19,20]; two of these used a single dose of 25 Gy[19,20] and another a total dose of 45 Gy in fractions from 15 Gy[9]. These data suggest that even with SBRT the use of very high doses per fraction is associated with a higher risk of severe late toxicity.

In the future, methods of integration between systems of stereotactic localisation and techniques of rapid and modulated irradiation (e.g. volumetric modulated arc therapy) (Figure 5) will allow a reduced risk of patient displacement during the single fraction and an improved dose conformity. These hybrid methods could perhaps reduce the negative impact of SBRT on the digestive system.

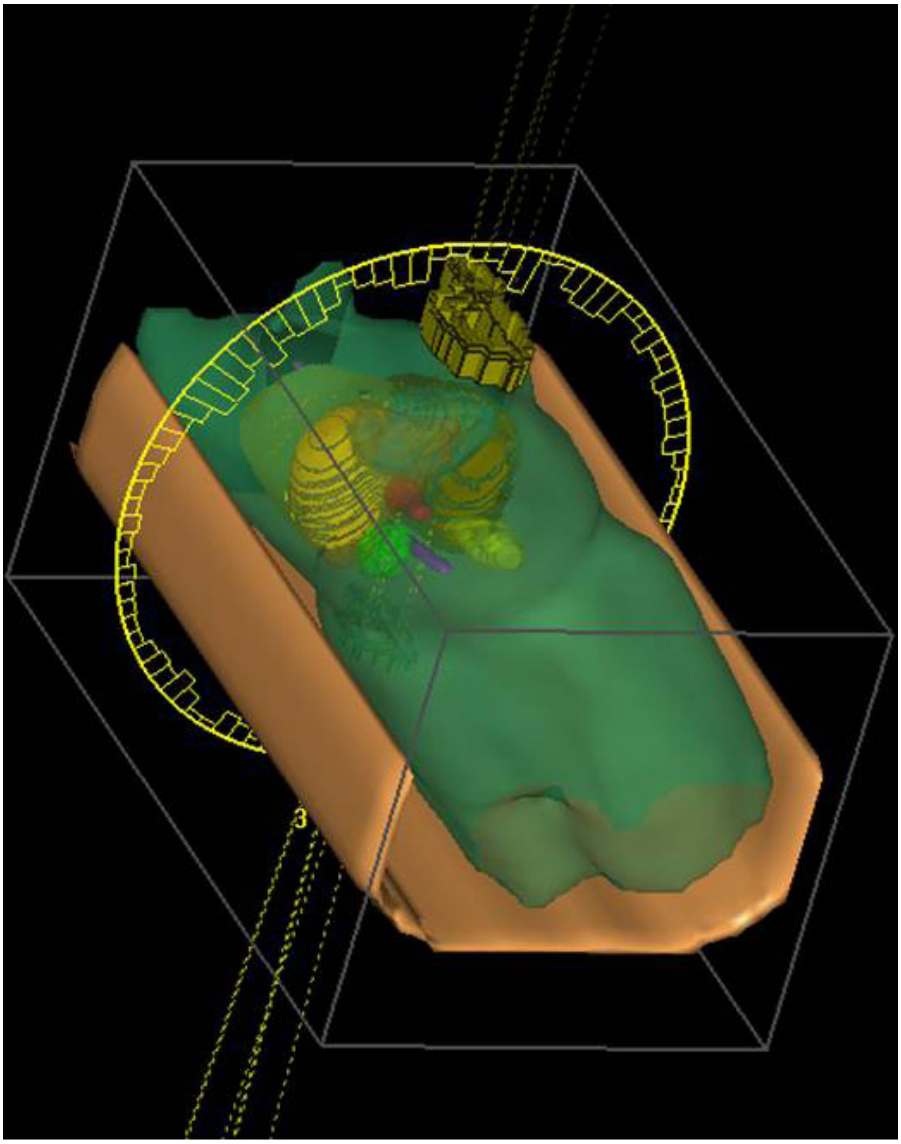

Figure 5: Irradiation geometry in an SBRT treatment using volumetric modulated arc therapy.

Conclusion

SBRT of pancreas carcinoma is a recent method with only preliminary data available. One of the main advantages is that SBRT, given its brevity, can be easily integrated with chemotherapy treatments. In particular, the ability to perform an SBRT treatment in 1–5 days may allow local tumour treatment without delaying the systemic therapy. The different series showed a relatively high rate of clinical responses and local control. The results in terms of survival are comparable with those of standard treatments based on prolonged RT and concurrent chemotherapy.

If further studies will be able to optimise this technique by reducing the side effects on the gastrointestinal tract, SBRT may have an increasing role in the treatment of this aggressive neoplasm.

Abbreviations list

CTV, clinical target volume; PTV, planning target volume; RT, radiotherapy; SBRT, stereotactic body radiotherapy.

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