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ORIGINAL ARTICLE

Stereotactic body radiotherapy (SBRT) in recurrent or oligometastatic pancreatic cancer

A toxicity review of simultaneous integrated protection (SIP) versus conventional SBRT

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Abstract

Background Stereotactic body radiotherapy (SBRT) in pancreatic cancer can be limited by its proximity to organs at risk (OAR). In this analysis, we evaluated the toxicity and efficacy of two different treatment approaches in patients with locally recurrent or oligometastatic pancreatic cancer.
Materials and methods According to the prescription method, patients were divided in two cohorts (C1 and C2). The planning target volume (PTV) was created through a 4 mm expansion of the internal target volume. In C2, a subvolume was additionally created, a simultaneous integrated protection (SIP), which is the overlap of the PTV with the planning risk volume of an OAR to which we prescribed a reduced dose.

Results In all, 18 patients were treated (7 with local recurrences, 9 for oligometastases, 2 for both). Twelve of 23 lesions were treated without SIP (C1) and 11 with SIP (C2). The median follow-up was 12.8 months. Median overall survival (OS) was 13.2 (95% confidence interval [CI] 9.8–14.6) months. The OS rates at 6 and 12 months were 87 and 58%, respectively. Freedom from local progression for combined cohorts at 6 and 12 months was 93 and 67% (95% CI 15–36), respectively. Local control was not statistically different between the two groups. One patient in C2 experienced grade ≥3 acute toxicities and 1 patient in C1 experienced a grade ≥3 late toxicity.
Conclusion The SIP approach is a useful prescription method for abdominal SBRT with a favorable toxicity profile which does not compromise local control and overall survival despite dose sacrifices in small subvolumes.

Keywords Local progression · Radiation therapy · Overall survival · Prognosis · Toxicity

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Stereotaktische Strahlentherapie (SBRT) beim wiederkehrenden oder oligometastatischen Pankreaskarzinom

Bewertung der Toxizität bei simultan integrierter Protektion (SIP) versus konventioneller SBRT

Zusammenfassung

Hintergrund Die stereotaktische Strahlentherapie (SBRT) ist bei Pankreaskarzinomen durch die enge Lagebeziehung der Risikoorgane (OAR) zum Zielvolumen erschwert. In dieser Analyse evaluierten wir die Toxizität und die Lokalkontrolle von zwei unterschiedlichen Therapiestrategien bei Patienten mit rezidivierendem oder oligometastatischem Pankreaskarzinom.

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Material und Methoden Die Patienten wurden anhand der Verschreibungsmethode in zwei Kohorten geteilt (C1 und C2). Das Planungszielvolumen (PTV) wurde durch eine Expansion des internen Zielvolumens (ITV) um 4 mm erzeugt. In C2 wurde zusätzlich ein Subvolumen (simultan integrierte Protektion, SIP) definiert, welches durch die Überlappung des PTV mit dem Planungsrisikovolumen (PRV) eines OAR generiert wurde, um die Grenzdosen für das jeweilige OAR einhalten zu können.

Ergebnisse Insgesamt 18 Patienten wurden behandelt (7 Lokalrezidive, 9 Oligometastasen, 2 kombiniert). Zwölf von 23 Läsionen wurden ohne SIP (C1) und 11 mit SIP (C2) therapiert. Bei einem medianen Follow-up von 12,8 Monaten lag das mediane Überleben bei 13,2 Monaten (95 %-Konfidenzintervall [KI] 9,8–14,6). Das Gesamtüberleben nach 6 und 12 Monaten betrug je 87 % und 58 %. Die Lokalkontrolle für das Gesamtkollektiv betrug nach 6 und 12 Monaten jeweils 93 % und 67 % (95 %-KI 15–36); sie war statistisch nicht unterschiedlich zwischen den beiden Gruppen. Ein Patient in C2 entwickelte eine akute Grad-4-Toxizität und 1 Patient in C1 entwickelte eine Grad-4-Spättoxizität.

Schlussfolgerung Die SIP-Verschreibungsmethode ist eine hilfreiche Strategie bei der SBRT mit einem günstigen Nebenwirkungsprofil. Trotz der Dosisreduktion in kleinen Subvolumina waren die lokale Kontrolle und das Gesamtüberleben identisch.

Schlüsselwörter Lokale Progression · Strahlentherapie · Gesamtüberleben · Prognose · Toxizität

Introduction

Pancreatic cancer has a devastating prognosis with 5-year survival rates of 7% [1]. Surgical excision is the treatment choice with a 5-year survival rate of approximately 20%, but resection is only possible in 15–20% of patients [2, 3]. Published data suggest that stereotactic ablative radiotherapy (SBRT) could be an alternative approach to chemoradiotherapy (CRT) for locally advanced pancreatic cancer (LAPC) with promising local control (48–94% at 12 months) [4–12]. Furthermore, reported local control for the treatment of hepatic metastases with SBRT ranges from 75–95% at 1 year and 60–90% at 2 years [13, 14].

With regard to toxicity, published data show an excellent acute tolerance but late gastrointestinal toxicity is dose-limiting [4, 15, 16] because of the close proximity to critical organs. Some authors introduced risk adaptive strategies, dependent on the location of the tumor, with reduced dose to the entire planning target volume (PTV) [15], while others prioritized the duodenal dose constraints over all other organs and accepted dose reductions to the total PTV [11].

By reducing the dose to the entire PTV, a severely reduced tumor control probability (TCP) has to be assumed as the price for lower normal tissue complication probability (NTCP). Other groups suggested the reduction of PTV margins [17]. In order to overcome the problem without reducing the dose to the whole PTV, we developed a novel prescription method termed simultaneous integrated protection (SIP) for quantifiable and comparable dose prescription to targets close to dose-limiting structures [18]. The current retrospective analysis was performed to analyze the toxicity and efficacy in patients who underwent SBRT for locally advanced or oligometastatic pancreatic cancer. We compared two cohorts without (C1) and with (C2) simultaneous integrated protection (SIP) for hollow organs in the vicinity of the target volumes.

## Materials and methods

Patient selection

This single institutional retrospective analysis was approved by the ethics board of the University Medical Center. Patients eligible for this study had histologically proven pancreatic adenocarcinoma (PDAC), had been deemed to be surgically or medically inoperable, and were discussed in a multidisciplinary board. A complete staging evaluation with physical examination, positron emission computed tomography (PET/CT) or magnetic resonance imaging (MRI) of the abdomen and CT thorax was performed prior to therapy. Treatment was according to our institutional standard operating procedures and in analogy to a planned single center phase I trial developed to test the toxicity profile of the SIP approach [18].

SBRT techniques

Patients were immobilized in supine position in a high precision customized vacuum cushion (BlueBAG BodyFIX, Innovative Technologies Völp, Innsbruck, Austria) using abdominal compression during 4D-CT (Brilliance CT Big Bore, Philips Medical Systems, Cleveland, OH, USA) or 4D-PET-CT (Gemini TF BigBore, Philips Medical Systems, Cleveland, OH, USA). For the four-dimensional (4D) acquisition, breathing motion was monitored with a belt (Mayo Clinic Respiratory feedback system) using a phase-based binning method. The internal target volume (ITV) was created accounting for the extent and the position of the tumor in all motion phases in three dimensions using the 4D image data. The PTV was a uniform 4 mm expansion of the ITV in all dimensions (both cohorts). All hollow visceral organs were expanded isotropically by 4 mm to demarcate volumes of increased risk of high dose exposure
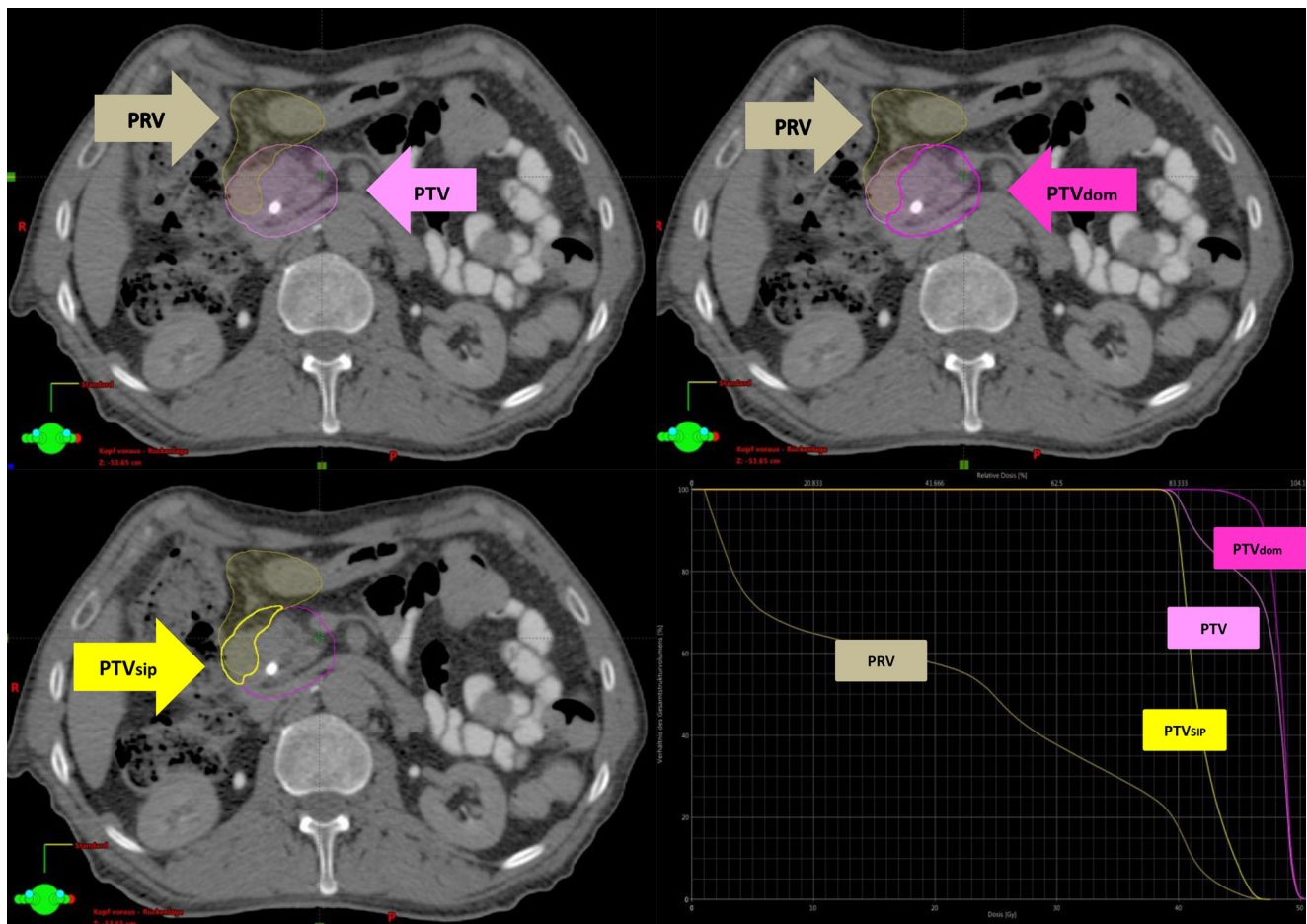
Fig. 1 Example of a treatment using the simultaneous integrated protection (*SIP*) method. *PTV*: Total planning target volume (104 cm^3), *PRV* planning risk volume, *PTV$_{SIP}$*: subvolume of the PTV with overlap of the PRV that was prescribed a reduced dose (21 cm^3), *PTV$_{dom}$*: subvolume of the PTV without overlap with the PRV

(planning risk volume, PRV). For lesions where dose constraints could not be achieved without reducing the dose to the whole PTV, we utilized a simultaneous integrated protection (SIP) dose prescription (C2), an intensity-modulated radiotherapy (IMRT) technique described in detail elsewhere ([18]; Fig. 1). In short, we defined a subvolume for the intersection of the PTV and the PRV of hollow organs termed simultaneous protection volume (PTV$_{SIP}$). The subvolume of the PTV without overlap with the PRV represented the dominant PTV (PTV$_{dom}$). The term dominant was chosen to imply that the SIP approach is only valid for small volumes of PTV$_{SIP}$. Dose was prescribed to PTV$_{dom}$ with a dose reduction made in the small PTV$_{SIP}$ subvolume. The dose in the PTV$_{SIP}$ was required to be as high as possible within the constraints to avoid local relapse. Treatment planning was performed using either Oncentra Masterplan (Nucletron BV [Elekta], Veenendaal, Netherlands) or Eclipse (Varian Medical Systems, Palo Alto, CA) treatment planning systems.

Patients were treated every other day with 3–12 fractions, depending on the proximity to OARs. Dose was prescribed either to a specific isodose (60%, 80%) or according to ICRU 83. Dose constraints were in concordance with the SIP protocol and published literature [18, 19]. Three fraction regimens were preferred in patients with lesions away from critical structures, 12 fraction regimens were preferred in patients with intimate contact to bowel structures, and 5 fraction regimens were intermediate in terms of closeness to the bowel. Daily on-line correction using cone beam CTs (CBCT) was applied with oral contrast in order to visualize the stomach and duodenum.

The prescribed doses were converted to biological effective doses (BED) and equieffective doses for 2 Gy fractions (EQD2), assuming that tumor and late reacting bowel tissue α/βratios were 10 Gy and 3 Gy, respectively.

Table 1 Patient and treatment characteristics

Gender	*No. of patients*
Male	10
Female	8
Median age, range	69 (37–79) years
Median CA 19–9 (range)	195 (6–4180) U/ml
Metastases before treatment	*No. of patients*
Yes	12
No	11
Prescription method	*No. of lesions*
C1	12
C2	11
Median PTV (cm^3)	43
C1	21 (6.6–106)
C2 Whole PTV	65 (11–210)
PTV$_{SIP}$	17 (0.4–66)
Median ITV (cm^3)	20 (2–114)
Median PTV dose (Gy)	37.5
C1	35 (30–40)
C2 whole PTV	48 (32–50)
PTV$_{SIP}$	42 (28–42)
Median BED$_{10}$ (Gy)	67
C1	60 (45–84)
C2 whole PTV	67 (46–100)
PTV$_{SIP}$	57 (28–60)
Median EQD2$_{10}$ (Gy)	56
C1	50 (38–70)
C2 whole PTV	56 (38–83)
PTV$_{SIP}$	47 (23–50)

SIP simultaneous integrated protection, *C1* non-SIP method, *C2* SIP method, *CA* cancer antigen, *PTV* planning target volume, *ITV* internal target volume, *BED* biological effective doses, *EQD2* equieffective doses for 2 Gy fractions

Fig. 2 Consort diagram (*LAPC* locally advanced pancreatic cancer, not primarily resected, *LR* local recurrence, *OM* oligometastases)

Toxicity and follow-up

Patients were examined clinically at least once per week during treatment by radiation oncologists. During follow-up, complete history, physical examination, and imaging (CTs, MRIs, or PET-CTs) were acquired every 3 months. Toxicity was scored using the National Cancer Institute Common Terminology Criteria for Adverse Events v. 4.03. Toxicities reported within 3 months after treatment completion were considered acute; any toxicity thereafter was considered to be late.

Statistical analysis

End points were toxicity assessment and freedom from local progression (FFLP) at 1 year; the latter was defined as the absence of progressive disease within the PTV, as well as overall survival. Local failure was defined as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Lesions that developed or progressed outside the PTV, in the same organ, were scored as local out of field progression and those developed in other organs as distant progression. Survival and control times were calculated from the start of SBRT. Time to progression and survival were evaluated with the Kaplan–Meier method and multivariate analysis using the Cox proportional hazards model and logistic regressions at a statistical significance level of $p \leq 0.05$ (two sided). Analyses were performed using SPSS (v. 21, SPSS Inc., Chicago, IL, USA).
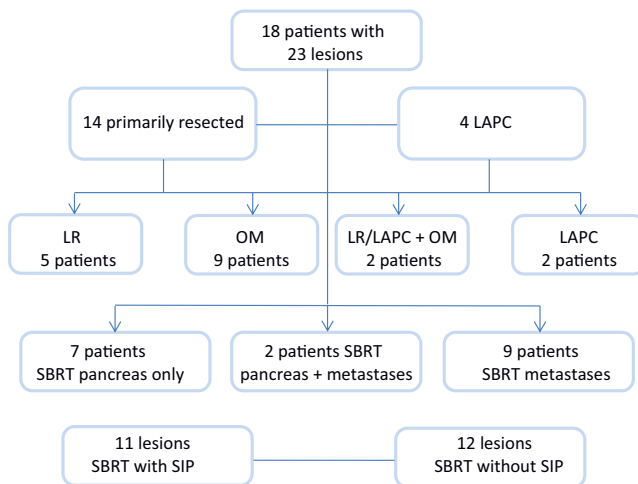
Results

Patients and treatment characteristics

Between 2009 and 2014, a total of 18 patients with 23 lesions were treated (Suppl. Table 1, Table 1). Nine patients were treated for local progression or recurrence after resected PDAC (3 and 6 patients, respectively), two of whom had an additional solitary metastasis (liver). Nine patients were treated for oligometastases (liver and/or lymph nodes). Of these lesions, 12 were treated without SIP (C1) and 11 were treated with SIP (C2, Fig. 2). Twelve patients were diagnosed with oligometastatic disease prior to treatment and 16 received systemic therapy prior to SBRT.

Patients in the C1 group received a median total physical dose to the PTV of 35 Gy (30–40 Gy), with a median BED$_{10}$ of 60 Gy (range 45–84 Gy) and a median EQD2$_{10}$ of 50 Gy (range 38–70 Gy). The median PTV volume was 21.3 cm^3 (range 6.6–106 cm^3).

In C2, the median PTV volume was 65 cm^3 (range 10.6–210 cm^3) and the median PTV$_{SIP}$ volume 17 cm^3 (range 0.4–66 cm^3). The median ratio of PTV$_{SIP}$/PTV was
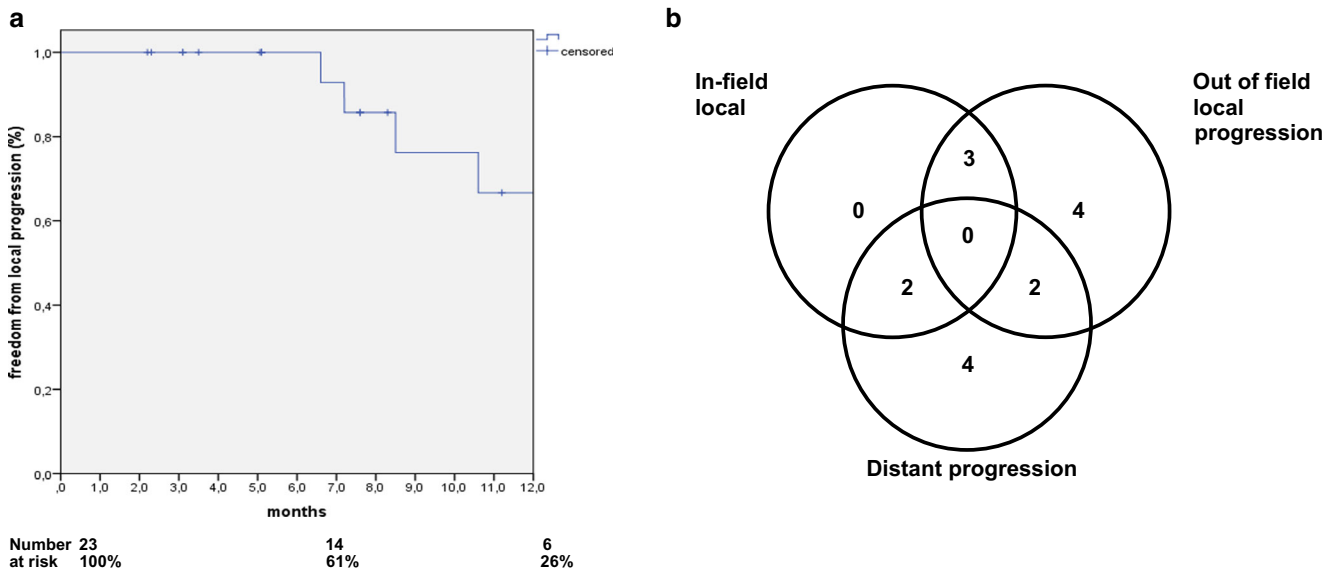
Fig. 3 **a** Freedom from local progression of the 23 lesions. **b** Venn diagram of sites of progression for all patients treated

12% (range 0.4–44%). The median total prescription dose was 48 Gy (range 32–50 Gy); the median PTV_{SIP} prescription was 42 Gy (range 28–42 Gy). The median biological effective dose (BED_{10}) and equieffective dose in 2 Gy fractions ($EQD2_{10}$) prescribed to the whole PTV were 67 Gy (range 46–100 Gy) and 56 Gy (range 38–83 Gy), respectively.

Response

After treatment, patients were routinely examined physically and received a CT or MRI every 3 months. In cases where the response could not be otherwise assessed, a PET CT was performed for further evaluation. Of the 23 lesions treated, 18 did not progress and 5 progressed in-field at a median interval of 7.7 months (range 6.6–13.7 months) after therapy. The FFLP at 6 months was 93% and at 12 months 67% (95% CI 15–35 months, Fig. 3). Neither use of the SIP technique ($p = 0.757$, log-rank), nor prior metastases, PTV volume, physical dose, $EQD2_{10}$, $D95_\%$, $D90_\%$ $D_{02,}$ D_{mean}, or corresponding $EQD2_{10}$ for PTV, PTV_{sip}, PTV_{dom} were significant for local control (Table 2). Of the 5 in-field uncontrolled lesions, three were treated with SIP and the remaining two without SIP. Sites of in-field progression were liver ($n = 2$), lymph nodes ($n = 1$), and pancreas ($n = 2$). Regarding the patterns of failure, no patient developed an in-field only progression; two patients developed an in-field in combination with an out of field but local (same organ, both in liver) progression and two in combination with a distant progression (Fig. 3). The median BED_{10} for the lesions that progressed was 67 Gy (range 53–86 Gy) and the median BED_{10} for the SIP subvolumes was 57 Gy (range 54–57 Gy) and the median BED_{10} for the

lesions that did not progress was 69.5 (range 46–119) and the median BED_{10} for the SIP subvolumes was 57 (range 43–60; $p = 0.458$). CA19-9 concentrations at start of SBRT were available in all but two patients and did not predict local failure ($p = n.$ s.).

Time to chemotherapy after SBRT was 3.6 months (median) from the last day of radiotherapy. A total of 14 patients had chemotherapy after SBRT and 3 patients had no further chemotherapy, data were missing in 1 patient.

Survival

At the time of the analysis 7 of the 18 patients had died, 5 from progressive disease and 2 from other causes. The median overall survival (OS) after treatment was 13.2 months (95% CI 16.3–34.5). The OS rates at 6 and 12 months were 87 and 58%, respectively. Survival from primary diagnosis was 34.9 months (range 9.2–88 months) postresection and 32.4 months (range 15.5–90.1 months) in patients with primary chemotherapy and oligometastases. Only the PTV volume was statistically significant for survival on multivariate analysis but not on univariate analysis (Table 2).

Toxicity

Toxicities are listed in Table 3. Most patients tolerated the treatment without or with mild symptoms (CTC grade I) mostly nausea (26%) and diarrhea (16%). One patient suffered from abdominal pain CTC grade 1 after the first fraction (1×9 Gy) and subsequently fractionation was changed to 10×4 Gy every other day. One patient (C2) suffered from an occlusive ileus (CTC grade 3) during radiotherapy due to tumor compression requiring a stent which resulted in

Table 2 A. Univariate and multivariate analysis for overall survival and freedom from local progression. B. Univariate analysis of relative dose parameters predictive of freedom from local control

A.

	OS UVA			OS MVA			FFLP UVA			FFLP MVA		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
C2 vs C1	0.51	0.11–2.32	0.3	0.24	0.01–6.72	0.4	0.74	0.11–4.76	0.8	0.72	0.02–27.6	0.8
Age	0.98	0.93–1.05	0.7	0.84	0.63–1.1	0.3	1.01	0.94–1.09	0.7	1.00	0.89–1.13	0.9
M1[a]	1.49	0.28–7.78	0.6	1.17	0.03–38.9	0.9	0.63	0.10–3.83	0.6	0.79	0.03–18.1	0.8
CA 19–9	1.00	1.00–1.01	0.2	1.00	0.99–1.05	0.1	1.0	0.99–1.00	0.4	1.0	0.99–1.01	0.2
PTV (cm^3)	1.01	0.99–1.03	0.1	1.05	1.00–1.01	0.05	0.99	0.96–1.03	0.9	0.97	0.91–1.04	0.4
ITV (cm^3)	1.01	0.98–1.05	0.2	–	–	–	1.00	0.96–1.05	0.7	–	–	–
PTV$_{sip}$ (cm^3)0.96	0.84–1.0	0.5	–	–	–	1.07	0.94–1.21	0.2	–	–	–
EQD2$_{10}$D$_{02\%}$	1.02	0.99–1.05	0.07	1.01	0.96–1.08	0.59	0.98	0.96–1.03	0.9	1.00	0.93–1.08	0.8

B.

		C1 Median (range) (Gy)	C2 Median (range) (Gy)	C1 OR	95% CI	p	C2 OR	95% CI	p
PTV	D$_{95\%}$	38 (29–47)	42 (24–47)	1.00	0.75–1.37	0.9	0.94	0.78–1.13	0.5
	EQD2$_{10}$ D$_{95\%}$	60 (36–91)	48 (36–65)	0.96	0.88–1.06	0.5	0.85	0.67–1.08	0.2
	D$_{mean}$	49 (30–59)	48 (39–55)	0.98	0.84–1.16	0.9	0.96	0.72–1.29	0.8
	EQD2$_{10}$ D$_{mean}$	90 (38–131)	59 (54–84)	0.98	0.93–1.03	0.5	0.91	0.75–1.11	0.4
	D$_{90\%}$	41(29–50)	42 (29–48)	1.01	0.78–1.32	0.9	0.86	0.66–1.11	0.3
	EQD2$_{10}$ D$_{90\%}$	66 (36–99)	52 (38–71)	0.97	0.89–1.05	0.5	0.66	0.37–1.18	0.2
	D$_{02\%}$	58 (31–67)	50 (46–61)	0.98	0.86–1.10	0.72	1.10	0.84–1.41	0.5
	EQD2$_{10}$ D$_{02\%}$	104 (39–163)	76 (58–90)	0.98	0.95–1.02	0.4	0.99	0.89–1.11	0.9
PTVdom	D$_{95\%}$	–	46 (38–49)	–	–	–	0.99	0.81–1.21	0.9
	EQD2$_{10}$ D$_{95\%}$	–	56 (53–76)	–	–	–	0.92	0.71–1.19	0.5
	D$_{mean}$	–	48 (42–55)	–	–	–	0.98	0.86–1.12	0.8
	EQD2$_{10}$ D$_{mean}$	–	67 (56–84)	–	–	–	0.92	0.92–1.02	0.3
	D$_{90\%}$	–	47 (39–50)	–	–	–	0.94	0.79–1.18	0.5
	EQD2$_{10}$ D$_{90\%}$	–	58 (53–78)	–	–	–	0.93	0.85–1.03	0.2
	D$_{02\%}$	–	50 (46–61)	–	–	–	0.97	0.89–1.10	0.9
	EQD2$_{10}$ D$_{02\%}$	–	76 (58–98)	–	–	–	0.98	0.95–1.01	0.3
PTVsip	D$_{95\%}$	–	39 (22–41)	–	–	–	0.99	0.81–1.2	0.9
	EQD2$_{10}$ D$_{95\%}$	–	44 (33–43)	–	–	–	0.92	0.71–1.19	0.5
	D$_{mean}$	–	42 (25–43)	–	–	–	0.99	0.79–1.23	0.9
	EQD2$_{10}$ D$_{mean}$	–	48 (38–54)	–	–	–	0.87	0.64–1.19	0.4
	D$_{90\%}$	–	40 (23–42)	–	–	–	0.99	0.81–1.22	0.9
	EQD2$_{10}$ D$_{90\%}$	–	45 (33–50)	–	–	–	0.91	0.70–1.18	0.4
	D$_{02\%}$	–	44 (33–47)	–	–	–	1.0	0.73–1.36	0.9
	EQD2$_{10}$ D$_{02\%}$	–	54 (51–66)	–	–	–	0.7	0.36–1.42	0.7

CI confidence interval, *NOS* not otherwise specified, *OR* odds ratio, *HR* hazards ratio, *SIP* simultaneous integrated protection, *C1* non-SIP method, *C2* SIP method, *OS* overall survival, *FFLP* freedom from local progression, *UVA* univariate analysis, *MVA* multivariate analysis

[a]Metastases prior treatment

Table 3 Acute and late toxicities

Acute toxicity	Grade CTC v4	No. of patients (%)	SIP
Nausea	1	5 (26)	Yes
Diarrhea	1	3 (16)	Yes
Fatigue	1	1 (5)	Yes
Abdominal pain	1	1 (5)	No
Mechanical ileus	3[a]	1 (5)	Yes
Gastrointestinal bleeding	3[a]		
Late toxicity	Grade CTC v4	No. of patients (%)	SIP
Hemorrhage	4	1 (5)	No

[a]same patient

termination of treatment at 31.5 Gy (7 × 4.5 Gy, $EQD2_{10}$ 38 Gy, and BED_{10} 46 Gy). The D_{mean} of the duodenum at the time of treatment interruption was 5.1 Gy; the D_{max} for 0.5cc was 20.5 Gy, for 5cc 18.3 Gy and for 10cc 16.5 Gy. A few days later the same patient suffered from an erosive bleeding from a Forrest III ulcer which was treated with proton pump inhibitors. The D_{mean} of the stomach at the time of treatment interruption was 5.6 Gy; the D_{max} for 0.5cc was 19.8 Gy, for 5cc 17.8 Gy and for 10cc 16.5 Gy.

There was only one late toxicity; one patient (C1) experienced a CTC grade 4 bleeding of the common hepatic artery, 9 months after SBRT in a region where the tumor was primarily infiltrating the vessel, which was successfully treated by radiological coiling of the vessel. At the time of bleeding the tumor showed a partial response but the patient simultaneously developed a peritoneal dissemination. The prescription dose to the tumor was 40 Gy (8 × 5 Gy at the 60% isodose, $EQD2_{10}$ 60 Gy, BED_{10} 72 Gy). The D_{mean} at the common hepatic artery was 66 Gy ($EQD2_{10}$ 106 Gy, $EQD2_3$ 164 Gy) and the D_{max} at 0.5cc was 66.7 Gy. No radiation-induced liver disease occurred.

Discussion

During the past years, several prospective and retrospective trials have tested the efficacy of SBRT in the treatment of LAPC with 1–15 fractions (4–25 Gy single doses) corresponding to an $EQD2_{10}$ of 31.25–204 Gy and a BED_{10} of 37.5–244.8 Gy [5]. Most acute toxicities were mild but several studies raised concerns due to a significant rate of gastrointestinal toxicities (ulcerations, bleedings, and perforations) [20]. The frequency of high-grade gastrointestinal toxicities (grade ≥ 3) rises over time [6] and ranges from 0–23 (median 7%).

These are the first published data reporting toxicity and outcomes with the novel SIP prescription technique described by Brunner et al. [18]. The treatment was very well tolerated without compromising the local control, despite of the prescription of a reduced dose to small subvolumes

(SIP). The two observed grade 3 acute toxicities (occlusive ileus and gastrointestinal bleeding) occurred during therapy in one and the same patient at a very low cumulative dose. Thus, we concluded that the mechanical ileus was due to tumor infiltration and the gastrointestinal bleeding probably through the manipulation due to prior stenting of the duodenum a few days before. There were no other grade ≥ 3 acute or late toxicities in patients treated with this method. One late toxicity occurred (CTC grade 4) in the C1 group, namely bleeding from the common hepatic artery. This vessel was previously infiltrated by the tumor prior to treatment; bleeding was completely resolved following coiling of the vessel. The observed late toxicities grade ≥ 3 of 5% after SBRT of the upper abdomen are in concordance with published literature (Table 4).

Murphy et al. [4] demonstrated a dose-dependent relationship of duodenal toxicity after single fraction therapy concluding that the multiple dose–volume histogram endpoints and a Lyman NTCP model are strongly predictive of duodenal toxicity. This dose-dependent relationship was also confirmed in other series [5, 20–23]. Some authors [5] reported that late toxicity grade ≥ 2 and grade ≥ 3 correlated highly with prescribed EQD2/BED after linear ($R2 = 0.85$ and 0.77, respectively) and Lyman–Kutcher–Burman modelling. Linear regression lines indicated grade ≥ 2 and grade ≥ 3 toxicity frequencies of 5% at 65 Gy and 80 Gy $EQD2_3$, respectively.

Several attempts were made to reduce the incidence of late toxicities. The Stanford group found significantly fewer occurrences of gastrointestinal toxicities with fractionated SBRT than with single fraction [10], while Schellenberg et al. [11] prioritized the duodenal dose constraints and accepted dose reductions in order to keep at least 50% of the duodenum near the PTV under the 50% dose and only 5% of the duodenum was allowed to receive 95% of the dose. Mahadevan et al. [15, 16] determined the fraction size for a total of three fractions by the distance between the tumor and bowel. The group reported a median OS of 20 months, although this was calculated from the time

Table 4 Published local control and toxicity reports

Author(year)	Fractionation	Total dose	EQD2$_3$	BED$_3$	mOS (months)	PFS (months)	LC (months)	Late toxicity
Gurka (2014 [24])	5 × 5 Gy	25	40	67	12.3[b]	6.8[b]	82%@6 m	G>3 8%
Koong et al. (2004 [9])	1 × 15 Gy 1 × 20 Gy 1 × 25 Gy	15 20 25	54 92 140	90 153 233	n.a.	n.a.	n.a.	No G≥3 toxicity
Murphy (2009 [4])	1 × 25 Gy	25	72.9	–	n.a.	n.a.	n.a.	G ≥ 3 8%
Mahadevan (2011 [16])	3 × 8 Gy 3 × 10 Gy 3 × 12 Gy	24 30 36	52 78 108	88 130 180	20[a]	15[a]	85%@21m (mFU)	G3 9%
Chuong (2013 [25])	5 × 7–10 5 × 5–6	35–50 25–30	70–130 40–54	117–216 67–90	16.4[a] 19.3 re-sected	9.7[a] 12.7 resected	81%@12m not re-sected	G ≥ 3 5.3%
Mahadevan (2010 [15])	3 × 8 Gy 3 × 10 Gy 3 × 12 Gy	24 30 36	52 78 108	88 130 180	14.3 [b]	9.6	n.a.	G ≥ 3 14%
Polistina (2010 [26])	3 × 10 Gy	30	78	130	10.6[a]	7.3	n.a.	No G3 tox-icity
Rwigema (2011 [27])	1 × 24 Gy (18–25)	24median	130median	216 median	10.3[c]	n.a.	48%@12 m	G3 4%
Tozzi (2013 [28])	6 × 7.5 Gy 6 × 6 Gy	45 36	95 65	157 108	11[b]	8[b]	91%@6m 77%@1 and 2 years	No Grade 3
Schellenberg et al. (2011 [11])	1 × 25 Gy	25	140	233	11.8[a] (50%@1y)	n.a.	94%@12m	G3 ≥ 5%
Chang et al. (2009 [6])	1 × 25 Gy	25	140	233	6.4[b] 4.7[d]	26%@6 m 9%@12 m	91%@6 m 84%@12 m	G ≥ 3 9%
Hoyer et al. (2005 [20])	3 × 15 Gy	45	162	270	5.7[a] (5%@1y)	4.8[a] 9%@12 m	n.a.	G ≥ 3 23%
Didolkar (2010 [29])	3 × 5–10	15–30	24–78	40–130	18.6[a], 8.6[b]	n.a.	91.7%	G ≥ 3 22% [e]
Goyal (2012)	1 × 20–25 3 × 8–10	20–25 24–30	92–140 52–78	135–233 88–130	14.4 m	11.4	65%@12m	G3 16%
Pollom et al. (2014 [10])	1 × 25 Gy 5 × 5 Gy	25 25	140 40	233 66	13.6[a] for all patients	n.a.	n.a.	G ≥ 3 12.3@12 m G ≥ 3 5.6@12 m
Herman et al. (2014 [2])	5 × 6.6 Gy	33	63	106	13.9 (1y59%)	n.a.	78%@12m	G > 3 6%
Moningi (2015 [31])	5 × 6.6 Gy 5 × 5 Gy	33 25	63 40	106 67	18.4[a]	9.8	n.a.	G ≥ 2 5.7
Mellon (2015 [32])	5 × 6–8 Gy	30–40	54–88	90–146	18.1	n.a.	78%@12 m LAPC	G > 3 7%
Comito (2016 [33])	6–7.5 Gy	45	94.5	157.5	13	8	90%@24 m	No G3 toxicity
Current study	–	37.5 median	70 median	116 median	13.2	n.a.	93%@6 m 67%@12 m	G3 5%
Summary	–	26	78	130	5.7–20[a] 6.4–14.3[b]	4.8–12.7[a] 6.8–8[b]	48–94@12 m	G ≥ 3 0–23% Median 7%

mOS median overall survival, *PFS* progression-free survival, *LC* local controlled, *mFU* median follow-up, *m* months, *G* grade
[a] Interval calculated from diagnosis; [b] Interval calculated from radiotherapy; [c] Interval calculated from local recurrence; [d] for patients with metastatic disease (19%); [e] 34% of the patients had prior radiation therapy

of diagnosis and late grade 3 toxicity was 9% (3/39 with gastrointestinal bleeding).

In our series the FFLP at 6 and 12 months was 93 and 67%, respectively, at a median $EQD2_{10}$ of 56 Gy and a BED_{10} of 67 Gy which correspond to the published data. The reported local control rates at 12 months ranged from 48–94% (Table 4). Furthermore, we could show an encouraging overall survival (OS) of 13.8 months in a patient collective with an unfavorable prognosis due to tumor recurrence and/or the presence of metastases at the time of treatment. The median OS in the SBRT series without metastases ranges from 5.7–20 months (median 14.4 months) from diagnosis and 6.4–14.3 months (median 11 months) from radiotherapy (Table 4). Over the past decades, the concept of oligometastases has emerged as an intermediate stage between locoregional tumor spread and disseminated metastases. Preventing or delaying local recurrence with SBRT not only decreases tumor burden but also offers palliative benefit. SBRT can be well tolerated without significant toxicity and may play a role in the prolongation of survival in highly selected patients. This group of patients with prolonged survival have a higher risk of developing late morbidities so that a calculated treatment approach is important in order to reduce the appearance of late toxicities but also to intensify treatment.

Conclusion

The SIP treatment approach is a useful adaptive prescription method which tailors the dose to each tumor, with a favorable toxicity profile, while respecting normal tissue constraints. Local control and overall survival were very good despite of dose sacrifices in small subvolumes in half of the patients. Based on these data, we are now conducting a phase 1 prospective study in patients with OARs adjacent to the PTV using the SIP concept.

Compliance with ethical guidelines

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