




Systematic Review

Stereotactic Radiotherapy for Critically Located Pancreatic and Biliary Targets: A Review on Simultaneous Integrated Protection and Other Dose-Painting Strategies to Minimize Dose to Critical Organs at Risk

Marco Lorenzo Bonù , Gloria Pedersoli, Jacopo Balduzzi *, Mariateresa Cefaratti, Eneida Mataj, Gianluca Cossali, Lorenzo Granello, Navdeep Singh, Vittorio Morelli, Davide Tomasini, Francesco Frassine, Paola Vitali, Fabrizia Terraneo, Luca Triggiani, Michela Buglione  and Stefano Maria Magrini 

Department of Radiation Oncology ASST Spedali Civili di Brescia, Brescia University, 25123 Brescia, Italy; marco.bonu@unibs.it (M.L.B.); g.pedersoli005@unibs.it (G.P.); m.cefaratti@unibs.it (M.C.)

* Correspondence: j.balduzzi@unibs.it



Citation: Bonù, M.L.; Pedersoli, G.; Balduzzi, J.; Cefaratti, M.; Mataj, E.; Cossali, G.; Granello, L.; Singh, N.; Morelli, V.; Tomasini, D.; et al. Stereotactic Radiotherapy for Critically Located Pancreatic and Biliary Targets: A Review on Simultaneous Integrated Protection and Other Dose-Painting Strategies to Minimize Dose to Critical Organs at Risk. *Radiation* **2023**, *3*, 98–109. <https://doi.org/10.3390/radiation3020009>

Academic Editors: Gérard Baldacchino, Eric Deutsch, Marie Dutreix, Sandrine Lacombe, Erika Porcel, Charlotte Robert, Emmanuelle Bourneuf, João Santos Sousa and Aurélien de la Lande

Received: 18 April 2023

Revised: 10 May 2023

Accepted: 12 May 2023

Published: 16 May 2023



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Simple Summary: Stereotactic Radiotherapy kills cancer cells through the precise delivery of high-dose radiation; however, the proximity with any organ(s) at risk might limit the delivery of an effective dose. This issue is particularly relevant for pancreatic and biliary tract lesions, given their proximity to the duodenum, stomach and bowel. Consequently, a reduction in the dose prescribed, causing a loss in tumor control, is frequent. One of the strategies to manage this problem is maintaining the high-dose prescription, while tailoring a dose reduction to the interface between target and any organ(s) at risk. This strategy was previously proposed in several small studies and needs to be validated on the basis of higher-quality evidence concerning safety and efficacy in pancreatic and biliary cancer.

Abstract: Background: Stereotactic Radiotherapy (SRT) in pancreatic and biliary tract cancer (PBC) suffers from proximity to any organ(s) at risk (OARs). Some strategies to manage this issue have previously been proposed, such as Simultaneous Integrated Protection (SIP), with the aim of maintaining a biological effective dose prescription while reducing toxicities. We performed a systematic review of the literature about SRT techniques applied in patients with tumor in proximity to OARs, with the aim of testing safety and efficacy. Methods: using PRISMA guidelines, we selected studies from a pool of more than 25,000 articles published from 2010 to 30 January 2023 that explored the use of SRT to deliver targeted treatment for PBC. We then selected the ones referring to decreases in prescription doses (for SRT only) in the area of overlap between planning target volume (PTV) and OARs. Local control (LC) and toxicities being detailed were exclusion criteria for articles. Results: 9 studies were included in our review, considering 368 patients. One-year LC probability ranges between 67% and 98.3% were reported. Late G3 toxicities ranged between 0% and 5.3%, while G4-G5 late toxicities were both reported as 0.3%. Conclusion: prioritizing critical OAR constraints limits severe toxicities while preserving LC in PBC SRT. Improving in-study reporting is essential to confirm these promising results.

Keywords: pancreatic cancer; biliary tract cancer; SRT; SBRT; simultaneous integrated protection

1. Introduction

Stereotactic radiotherapy enables the delivery of high-dose medication to the tumor in a relatively small number of fractions (1 to 8), potentially overcoming radio-resistance of some histological cancer subtypes.

In SRT, the therapeutic ratio is optimized through the delivery of highly conformal dose distributions with steep dose fall-off, with the aim being obtaining an optimal absorbed dose in a target volume combined with minimal normal tissue irradiation.

Traditional dose prescriptions follow ICRU 83 recommendations, with the goal being dose homogeneity. SRT led to a new paradigm concerning both technique and radiobiology; thus, ICRU 91 was published in 2017 to guide physicians and physicists in the task of optimization of the SRT process [1].

Inhomogeneity in dose prescription is frequently a goal of SRT, although ICRU report 91 does not specify the optimal dose inhomogeneity within the planning target volume (PTV), as there are no explicit constraints provided on the maximum dose inside of PTV. In fact, there is a lack of consensus on the most relevant dosimetric parameters influencing local tumor control. Authors suggest that near-minimum, near-maximum, median or mean PTV/clinical target volume (CTV)/gross tumor volume (GTV) doses might be the most important parameters related to tumor control, but these are suggestions are still open to question [2–4].

One of the unanswered major points in SRT and high-dose radiotherapy is represented through the cases in which organs at risk (OARs) are located near to the PTV or even overlapped to the target. Due to the increase in SRT indications, along with the new technical possibilities, physicians are facing these challenging situations more frequently.

The upper abdomen represents the paradigm for planning complexities, given the presence of frequent tumor abutments near critical OARs, tumor motion, OARs motion (frequently not dependent or only partially dependent to tumor motion) and the intrinsic radiosensitivity of the majority of the visceral OARs in this region. Such planning complexities are typical but not limited to the upper abdomen; in fact, ultra-central thoracic targets, mediastinal, juxta-esophageal lesions, lower abdominal, brain and head and neck lesions could present a critical relationship with OARs that limits the delivery of safe and effective SRT.

It is clear, therefore, that management of lesions near critical OARs represents one of the most important and critical questions to be answered in modern SRT.

Some of the strategies proposed to face this clinical–dosimetric dilemma rely either on the prescription of reduced total dose to the entire PTV or escalating the dose prescribed to GTV while accepting a reduced PTV coverage [5,6]. One solution to this problem is to plan how to use simultaneous integrated protection (SIP), a concept in which the dose constraint of an OAR near the target commands the prescription in the area of overlap between the target and OAR. SIP is, therefore, a deliberated way to deliver the maximum allowed dose to the overlap area (the so-called SIP volume), while maintaining higher dose in the area “far” from critical structures [7]. SIP concept could be used both for moderately hypofractionated RT and SRT [8–10].

Concisely, this approach requires accurate definitions of the volumes to be treated. GTV, CTV, internal target volume (ITV), and PTV are defined in accordance with the ICRU reports 50 and 62. For the OARs, authors precisely defined a dose-limiting OAR, its internal margin contoured in 4D CT phases and the relative PRV. PTV and SIP correspond to the intersection between PTV and PRV of critical OARs, while the rest of PTV is named Dominant PTV. Figure 1 reports an example of planning exploiting the SIP concept.

Comparable but less structured approaches are used, such as the strategy of cropping PTV overlapped with OARs, or maintaining PTV, despite the overlapping volume, without requirements to overcome OAR dose constraints. However, using a less defined method leads to a lack of replicability and comparability in data concerning quality of plans and OAR doses.

One of the advantages of using SIP approach is represented via the formalization of dosimetric goals in overlap area, with the possibility of quantifying and comparing dosimetric trade-off between plans [11]. On the other hand, one of the most critical aspects of SIP planning is represented via the uncertainty in tumor control in the area of dose

reduction. In fact, SIP planning is complex and time consuming and does not completely preserve against the risk of toxicity.

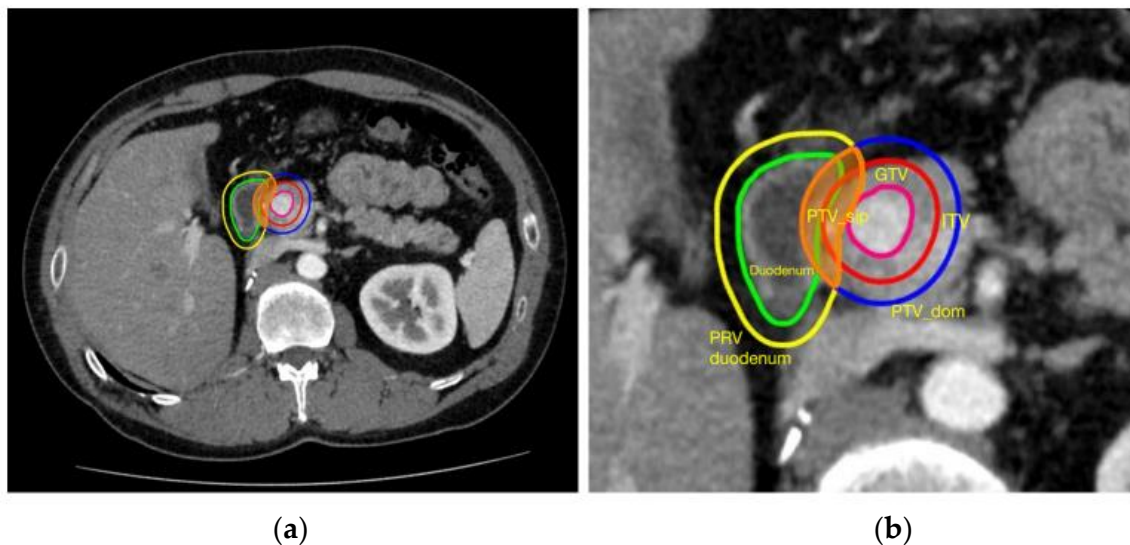


Figure 1. (a) An axial CT scan slice illustrating an example of SIP planning application. (b) Focus on volumes of interest for SIP concept (duodenum as organ at risk (green); PRV_duodenum: planning risk volume of duodenum (yellow); GTV: gross tumor volume (pink); ITV: internal target volume (red); PTV_dom: planning target volume_dominant (blue); PTV_sip: planning target volume_simultaneous integrated protection (filled orange)).

Despite the great importance of the issue, only a small amount of data addressing the clinical results in SIP planning are available, and such data are frequently represented via small mono-institutional series [12]. In this review, we selected studies that discuss the role of SIP in SRT planning with a focus on local control probability and late toxicity. Moreover, we analyzed and discussed the possible applications in SIP planning, as well as the potential advantages and pitfalls of this technique. Nevertheless, given the lack of standardized planning prescription goals in such a clinical scenario, the analysis also included studies that did not explicitly use SIP planning concepts but prescribed a tailored reduced dose to preserve critical OARs.

2. Material and Methods

2.1. Search Strategy

We performed a review of the literature following PRISMA guidelines [13]. A systematic literature search was performed using the MEDLINE (via PubMed) and EMBASE electronic data bases. We used a search algorithm based on a combination of terms: high dose radiotherapy OR SBRT or stereotactic body radiotherapy OR SRT or stereotactic radiotherapy OR critical organ OR SIP or simultaneous integrated protection OR lesion near critical organs at risk OR pancreatic cancer high dose radiotherapy OR upper abdomen high dose radiotherapy OR abdomen high dose radiotherapy.

The search was maintained up until 30 January 2023. Only articles in English were selected, while pre-clinical and non-in vivo studies, conference proceedings, editorials and reviews were excluded. To expand our search, references of the retrieved articles were also screened for additional studies.

2.2. Study Selection

Two researchers (G.P. and J.B.) independently reviewed the titles and abstracts of the retrieved articles. Three researchers (G.P., J.B. and M.B.) then independently reviewed the full-text version of the remaining articles to determine their eligibility. Inclusion criteria were as follows:

- Patients > 18 years old;
- Studies from 2010 to 2023 that performed SRT in patients with target lesions near critical OARs. Suitable SRT criteria consisted of prescription doses of at least 35 Gy in five fractions, delivered with volumetric-modulated arc therapy (V-MAT), IMRT, Helical IMRT or Robotic IMRT;
- For use of SIP as planning strategy, the planning process had to be clearly described in material and methods sections; the keyword “SIP” was not necessary, but dose prescription had to be decreased in the area of overlap between PTV and OAR as in the SIP process;
- A report about target coverage (at least PTV and GTV) and dose constraints for critical OARs;
- Selected studies had to include clinical and radiological information about follow-up for toxicity assessment, as well as information concerning local control.

2.3. Study Endpoints

Primary endpoints of the study were local control and late toxicity. Local control was defined following RECIST 1.1 criteria [14], while late toxicity followed the common terminology criteria on adverse events version 5.0 (CTCAE 5.0) and secondary endpoints were acute toxicity, progression free survival (PFS) and overall survival (OS).

3. Results

Figure 2 presents the search methodology and results. A total of 26,375 articles were extrapolated from a first computer literature search; after applying inclusion criteria, 2931 records remained. After the review of titles, abstracts, and full text, 2931 records were excluded (2580 did not consider high dose RT for targets near critical organs at risk, 290 did not consider high dose RT, and 52 did not perform any kind of dose reduction to mitigate dose-to-critical OARs). A total of nine articles were finally included in the systematic review. Table 1 summarize the results of the search strategy.

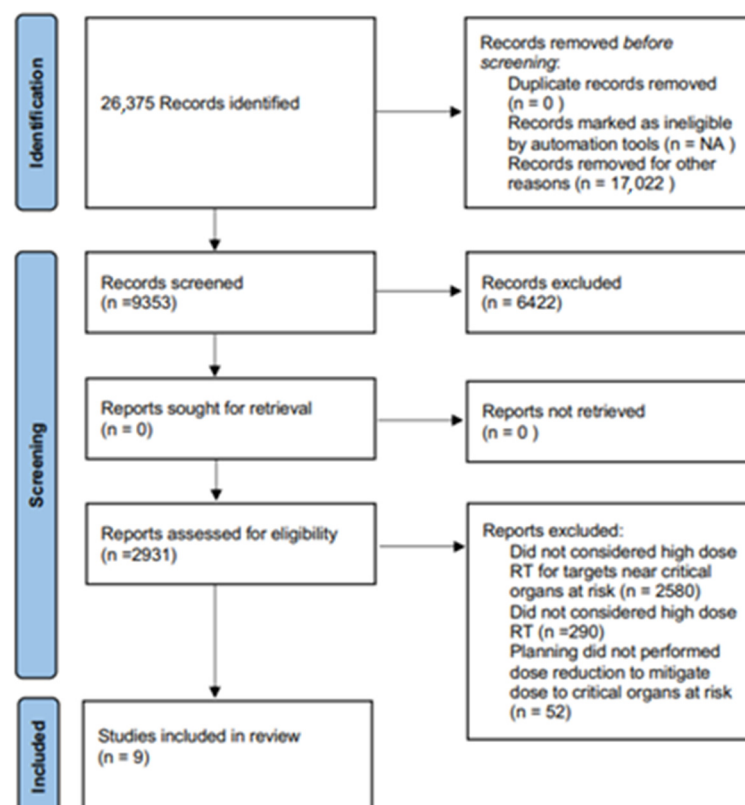


Figure 2. PRISMA process representing search strategy.

Table 1. Summary of studies included in review process.

Study	Year	Target Site	N° pts	Methodology	Acute \geq G3 (n°—(Grade))	Late G2	Late G3	Late G4	Late G5	FFLR (L.C.)
Brunner et al. [7]	2016	Pancreas	2	SIP		N.R.	0	0	0	100% at 8.6 months
Gkika et al. [15].	2017	Pancreas	9	SIP (SIP and without-SIP group)	2—G3	N.R.	0	0	0	67% at 1-year
Comito et al. [16]	2016	Pancreas	45	Priority to OARs	0	2	0	0	0	90% at 2-year
Simoni et al. [17]	2020	Pancreas	59	SIB/SIP	0	N.R.	0	0	0	79.7% at 1-year (unresected pts)
Suker et al. [18]	2019	Pancreas	39	Priority to OARs	1—G3 1—G4 2—G5	N.R.	1	1	0	Median 20 months
Tozzi et al. [19]	2013	Pancreas	30	Priority to OARs	0	0	0	0	0	85% at 1-year
Choung et al. [20]	2013	Pancreas	73	Priority to OARs/SIB	0	0	4—5.3%	0	0	81% at 1-year (unresected pts)
Chuong et al. MRI-guided [21]	2020	Pancreas	35	OAR priority	1—G3	1	1	0	0	87.8% at 1-year
Chuong et al. (update) [22]	2022	Pancreas	62	OAR priority	3—G3	N.R.	2	0	1 (possible)	98.3% at 1-year
Franzese et al. [23]	2019	Biliary tract	14	OAR priority	2—G3	0	0	0	0	76.7% at 1-year

In their seminal paper, Brunner et al. reported a small series of patients treated with SIP planning modality. The key inclusion criterion in this study was met when there was an overlap between PTV with either an OAR or its expansion, causing a reduction in the dose prescription in such an area (i.e., SIP area) in order to limit the risk of unacceptable toxicity to the OAR.

In this single-center phase I trial, six patients were enrolled with indications for SBRT of targets close to OAR. Patients underwent 4D treatment planning imaging with custom immobilization devices. Two out of five patients presented a pancreatic target. Only one patient was treated with a non-SIP plan, with the dose being reduced to treat the central lung metastasis, close to the right hilum; all other patients were treated accordingly with the SIP concept. After a median follow-up of 8.6 months, local control was 100%, and no toxicities \geq G3 were registered. OS data were not reported [7].

A single institutional retrospective analysis was conducted by Gkika et al. regarding patients with locally recurrent or oligometastatic pancreatic cancer treated with SBRT. According to the prescription method, patients were divided in two cohorts: C1 without SIP and C2 with SIP approach.

Between 2009 to 2014, 18 patients with 23 lesions were treated: 12 patients were placed in C1 group, while 11 patients were treated with the SIP approach. Planning for SIP was conducted according to Brunner et al.'s method. Patients were treated every other day with 3–12 fractions, depending on the proximity to OARs.

End points were acute and late toxicity, one-year FFLR and OS.

In C2 SIP group, median total prescription dose was 48 Gy (range 32–50 Gy); the median PTV_SIP prescription was 42 Gy (range 28–42 Gy).

After a median follow-up of 12.8 months, the resulting FFLR was 67% at the 1-year stage, median OS was 13.2 months and OS probability was 58% at the 1-year stage.

Regarding toxicity, during the treatment, the authors observed two G3 acute toxicities (occlusive ileum and GI bleeding), while there were no G4 or higher acute toxicities in the SIP group. In the non-SIP group, one late toxicity was observed (bleeding from the previously infiltrated common hepatic artery) (G4) [15].

Comito et al. enrolled 45 patients with histologically proven LAPC treated with SRT in a prospective, observational, single-arm, and single-institution phase 2 trial. A total dose of 45 Gy was delivered in six consecutive daily fractions. Considering dose-volume constraints for OARs, such as D1 cc < 36 Gy for duodenum and D3 cc < 36 Gy for stomach and small bowels, the dose distribution was optimized to achieve a target coverage of V95% = 100% for the CTV; for the PTV, a lower priority was set than for the OAR constraints.

After a median follow-up period of 13.5 months, FFLR was 90% at the 2-year stage. Concerning toxicities, no patients experienced perforation, ulcer, bleeding, or other acute or late grade 3 toxicity or higher. Two patients experienced grade 2 late gastritis, confirming the safety of this SBRT regimen. The median OS at the end of SRT was 13 months, with 1- and 2-year OS rates of 59% and 18%, respectively. When calculated from the diagnosis, OS was 19 months with 1 and 2 years OS of 85% and 33%, respectively [16].

Simoni et al. enrolled 59 consecutive patients (27 borderline resectable and 32 locally advanced) treated with SRT for Pancreatic Ductal Adenocarcinoma. In total, 58 patients (98.3%) completed the planned treatment consisting of delivery of 30 Gy to the PTV with a simultaneous integrated boost to the tumor–vessel interface. In the overlap area between PTV and planned OAR volume, the dose was lowered to 25 Gy. A further 35 patients (59.4%) received surgical resection afterwards. The dose–volume constraints for dose-limiting OARs were as follows: for duodenum, stomach and bowel, the volume receiving 30 Gy must be lower than 5cc, while the mean dose to the critical organ less than 20 Gy.

After a median FU of 15.1 months, 1- and 2-year FFLR were 85% and 80% versus 79.7% and 60.6% in resected and unresected patients. A further 20 patients (33.9%) suffered from G1-2 acute toxicity, while no G \geq 3 adverse events were observed, neither acute or late.

The median OSd (from the date of diagnosis) of the entire cohort was 30.2 months, with 1- and 2-year OSds of 95% and 72.5% in resected patients versus 97% and 49% in non-resected patients, respectively. Median OSsrt (from the date of SBRT) was 19.1 months [17].

Suker et al. enrolled 50 patients in their trial. Patients received eight cycles of FOLFIRINOX, and if no evidence of tumor progression was observed, they also received SRT afterward at total dose of 40 Gy in five daily fractions, up to PTV at 80% isodose line. At least 95% of the prescribed dose should cover 95% of the PTV, although priority was given to the OAR constraints. SRT was delivered with robotic IMRT with real-time tumor tracking performed using the Synchrony respiratory motion tracking system with gold fiducial markers implant. The dose–volume constraints for dose-limiting OARs were as follows: bowel, duodenum and stomach near-maximum dose we supposed to be maintained at less than 35 Gy. Nineteen (38%) patients did not receive all eight cycles of chemotherapy. Thirty-nine (78%) patients completed the scheduled treatment with SRT.

Median FFLR was 20 months in patients treated with SRT. Two (5%) grade 3 or 4 adverse events after SRT were observed. Within 3 months after SRT, two deaths (5%) occurred due to GI bleeding. The six (12%) patients who underwent surgical resection were all R0; two of them had a pCR. Concerning OS, the median OS was 15 months. For those who completed SRT, the 1-year OS rate was 79%, rising to 83% for patients who also underwent surgery. Median OS in patients who did not receive SRT reduced to 7 months. Median OS after starting SRT was 10 months [18].

Tozzi et al. reported the outcomes of 30 patients with unresectable or recurrent pancreatic adenocarcinoma who underwent exclusive SRT.

A total dose of 45 Gy was delivered in six consecutive daily fractions. Required target coverage was $V_{95\%} = 100\%$ for the CTV and, ideally, for the PTV, but with priority for OARs constraints when overlap between PTV and OAR occurred. In those cases, the dose was lowered to 36 Gy in six daily fractions. SBRT was delivered with VMAT technique.

The dose–volume constraints for critical OARs were: as follows duodenum: $D1cm^3 < 36$ Gy; and stomach and small bowel: $D3cm^3 < 36$ Gy;

A total of 25 patients (83%) were treated with 45Gy in six fractions. In five patients (17%), the dose prescription was reduced to 36 Gy in 6 fractions not to exceed dose constraints of duodenum and stomach. Overall, FFLR was 85% and 77% after 1 and 2 years, respectively. In the group of patients treated with dose prescription of 45 Gy, FFLR was 96% at 1 and 2 years, with a single case of local progression. Median OS after calculation from SRT was 11 months, while 1 year OS was 47%.

Twelve patients (43%) suffered from acute G1 fatigue, five (25%) experienced G1 nausea, and three (10%) received ondansetron as antiemetic drug for G2 nausea. After 1 month, none of these patients had persistent nausea. Three (10%) suffered from G2 pain, while no acute or late $G > 3$ toxicities were observed [19].

In Chuong et al.'s study, 73 patients with locally advanced and borderline resectable pancreatic cancer were treated with SRT delivered in five consecutive fractions using dose-painting technique delivering 7 to 10 Gy/fractions simultaneously to the region of vessel abutment or encasement and 5–6 Gy/fraction to the remainder of the tumor. Normal tissue constraints for critical OARs were as follows: duodenum/small bowel/stomach maximum 35 Gy, mean < 20 Gy, V_{30} Gy < 5 cc, V_{35} Gy < 1 cc, planning objective consisted in prioritization of OARs constraints.

After a median follow-up of 10.5 months, 34 patients were resected. One-year FFLR was 81% in non-resected patients and 100% in resected patients.

Concerning toxicity, no acute $G \geq 3$ toxicities were observed, while four patients (5.3%) suffered from late G3 toxicity (three and one patients experienced GI bleeding and anorexia, respectively, with the latter case requiring placement of a feeding tube). One of these patients also experienced local tumor progression into the duodenum, making it unclear if bleeding resulted from disease progression, treatment toxicity or both. No late G4-5 toxicities were observed.

Median OS and 1-year OS for the BRPC and LAPC patients were 16.4 vs. 15 months and 72.2% vs. 68.1% (all $p > 0.10$). Patients who underwent surgical resection had significantly improved median OS (19.3 vs. 12.3 months; $p = 0.03$) and 1-year OS (84.2% vs. 58.3%) compared to non-resected patients [20].

Choung's group also published a further mono-institutional retrospective series including 35 patients treated with MR-Guided IMRT on MRI-linac accelerator for locally advanced and borderline resectable pancreatic cancer after induction chemo. Dose prescription was 50 Gy in five consecutive fractions, while any overlapping point portion of GTV or PTV through the OARs PRVs was constrained to 35 Gy. Elective nodal irradiation was performed in 20 patients.

Dose constraints for critical OARs were as follows: for the stomach/duodenum/small bowel V35 Gy < 0.5 cc, V40 < 0.03 cc; large bowel V38 < 0.5 cc, V43 < 0.03 cc.

After a median FU of 10.3 months, 1-year FFLR was 87.8%.

Concerning toxicities, acute grade 2 (nausea and anorexia) occurred in three patients (8.6%), while acute grade 3 (diarrhea) occurred in one patient (2.9%); late toxicities occurred in one case (2.9%) of G2 duodenal bleeding and one case of G3 bile duct stenosis, requiring percutaneous drainage. No grade 4 or 5 cases were registered. Median OS was 9.8 months and the 1-year OS was 58.9% (51.6–65.1%) [21].

The authors performed an updated analysis of their previously published institutional experience concerning MRI-guided SRT in inoperable pancreatic cancer after induction chemotherapy. The treatment planning and delivery approach remained the same as the method outlined in the previously discussed publication. A total of 62 patients were enrolled, with 55 having tumors in the top of the pancreas. Patients were treated with a median dose of 50 Gy for five consecutive days. Doses of 40 Gy (2 patients—3.2%) and 45 Gy ($n = 5$ —8.1%) were prescribed to a small group of patients; if no severe toxicity was observed, the dose was increased to 50 Gy. Median follow-up for all patients was 18.6 months from diagnosis and 11.0 months from start of radiation therapy. Median FFLR from diagnosis was not reached, while 1- and 2-year FFLR from diagnosis were 98.3% (94.8–100%) and 87.7% (77.0–98.3%). Median OS from diagnosis was 23 months (18.0–29.0). Moreover, 1- and 2-year OS from diagnosis were 90.2% (82.7–97.6%) and 45.5% (31.5–59.5%).

Acute G3 toxicity occurred in three patients (duodenal stenosis, abdominal pain). Acute G4 and G5 toxicity events were not registered. Late G3 toxicity (4.8%) consisted of two patients with GI bleed that resolved with transfusion. One patient died due to a gastroduodenal artery bleed that was not definitely related to SRT (possible grade 5) [22].

Franzese et al. performed a retrospective analysis of a cohort of 51 metastatic biliary tract cancer (mBTC) patients treated with SRT for oligometastatic disease from 2008 to 2017. Of the 51 patients, targets for whom a reduction in dose prescription was necessary were represented via 4 cases of extrahepatic biliary tract relapse, 6 cases of nodal lesion near duodenum and stomach and 4 cases of hepatic lesions with a critical relationship with colon. The median delivered dose was 45 Gy (range 40–75) in 3–5 fractions. Dose prescription was reduced in the area of overlap between critical OARs and PTV based on the following dose constraints: duodenum was D1 cc < 36 Gy, while stomach and small bowels were D3 cc < 36 Gy.

After a median follow-up of 14 months, FFLR was 26.8 months and 1-year FFLR was 76.7%.

Ten patients reported grade 1–2 toxicity (fatigue, nausea, increased liver enzymes and hyperammonemia) and two cases of acute G3 biliary obstruction (with a schedule of 45 Gy in 6 fractions and 54 Gy in 6 fractions). No late toxicities were registered.

Median OS was 13.7 months with a survival probability after 1 and 2 years of 58% and 41%, respectively [23].

4. Discussion

Our review shows that dose reduction is a strategy used in highly experienced centers to maintain ablative dose prescription when treating targets near critical OARs.

Despite the heterogeneity in dose reduction strategy beneath studies, pancreatic-biliary SRT tailoring dose in respect to critical OARs constraints was proven to be safe and effective. Expected late G3 toxicity ranged between 0% and 5.3%. One-year local control probability ranged between 67% and 98.3%, and the studies that also report FFLR at 2-years describe durable results in a range between 60.6% and 90%. Considering 368 patients in our analysis, rates of G4 and G5 late toxicities were both around 0.3%, with a single patient in Choung's analysis for whom death was not surely correlated with the SRT, and a single patient in Suker's study who suffered from G4 late toxicity. In this trial, two G3–G4 acute toxicities were also reported, while two patients died due to gastro-intestinal bleeding within 3 months of SRT. Although our primary endpoints were late toxicities and FFLR, a proper analysis of these severe acute events will follow afterwards, given the importance of this data.

Reaching a high therapeutic ratio is particularly relevant in pancreatic cancer. Biology of pancreatic ductal adenocarcinoma is characterized by high propensity to metastatic spread, and the role of SRT in improving OS still needs to be demonstrated. Conversely, some reports seem to show an increase in outcomes for those treated with SRT, compared to normofractionated Radio-chemotherapy. In such context, optimizing safety profile and effectiveness of a local treatment could preserve the patient's PS without limiting the compliance to systemic therapy.

Seminal studies showed high efficacy of single- and three-fraction schedules but unacceptable rates of GI late toxicity, such as hemorrhage, ulceration, perforation and stenosis [24–28].

Remarkably, in these experiences, the dose prescribed was not decreased in order to respect duodenum and stomach dose-constraints. Pancreatic SRT moved, therefore, to test safety and efficacy of 5- and 6-day schedules.

A reduction in serious GI adverse events was achieved while maintaining encouraging local control rate; however, G4-5 toxicities remained a concern in some series, especially for studies that did not prioritize doses to critical OARs [20,29–31].

Some important considerations about dose constraints and toxicities risks need to be emphasized. In fact, reconstructing a cause–effect relationship is difficult in pancreatic-biliary SRT. Organ motion is complex and depends on respiratory-induced motion and bowel spontaneous activity. Moreover, it is unlikely that tumor motion is always consistent with OAR motion. Such considerations, together with huge differences in planning (contouring for OARs, target, dose prescription) between centers, make difficult to depict a clear dose relationship for bowel toxicities. An intriguing example of such complexity is showed in a sub-analysis of the trial of Suker and colleagues, which tried to address the inter-fractions dose discrepancies for critical OARs between provisional plans and plans of-the-day thanks to an on-rail CT scan before SRT. The analysis clearly showed a significant increase in dose to critical OARs concerning maximum but also intermediate doses [32]. Moreover, intra-fraction motion is another fundamental point to address in pancreatic-biliary SRT. MRI-guidance and breath hold are considered new promising techniques to manage and limit uncertainties, hopefully reducing trade-off between target and OARs [33].

Another important point is the frequent omission of dose constraints concerning intermediate doses in some studies. Some authors suggest a relationship between both near-maximum and intermediate doses and the risk of developing late-duodenal toxicity [34].

Concerning the quality of the available evidence, one of the major issues that our review clearly shows is that dose reduction strategies in SRT planning are heavily under-reported. Some experiences clearly declare the reduction in dose prescriptions and the methodology used, while others declare an OAR constraint priority or reduction in PTV dosimetric coverage in case of challenging situations. Therefore, the interpretation and replicability of some studies could be difficult.

Despite these uncertainties, results of this review suggest that moving to fractionated SRT is not sufficient to prevent severe GI late toxicities. Planning objectives need to be

strictly decided ab initio, and a strategy consisting in tailoring the dose in the area of overlap between PTV and critical OARs seems to be feasible and guarantee fair results in terms of late toxicity while preserving local control in the context of pancreatic-biliary cancer.

Taken together, SIP planning and the “OARs priority strategies” seem to guarantee a concrete reduction in expected toxicity versus the standard approach. However, no robust conclusion must be made concerning other crucial questions related to this kind of prescription modality:

- Is there a loss of tumor control probably due to these approaches? If yes, is it related to the volume of PTV_SIP (i.e., greater area of overlap = greater area of dose reduction) or related to other clinical-dosimetric factors?
- If relapse occurs, is it in SIP/dose reduction area?
- If relapse is not in SIP area or does not occur, which biologic mechanism could also explain the tumor control in case of non-ablative doses delivered?
- Is it safe and useful compared to the ICRU 91 and SIP approach prescribing extremely high doses in the area of PTV relatively far from critical OARs, as suggested by some authors? (The so-called “combined SIB/SIP approach”)?

Answering these questions is crucial in guiding the future of high-dose radiotherapy in proximity to critical OARs. In fact, SIP planning is heavily time-consuming for the whole radiotherapy facility as it needs to be justified on the basis of more robust evidence concerning safety and efficacy.

Future studies might give an answer to the previously reported question. Their design should be carefully balanced to clarify the eventual advantage of SIP approach from clinical and biological points of view. We suggest planning SRT targets near critical OARs, exploiting the prescribing and recording scheme conceived by Brunner et al. (rather than simply using an OAR priority approach) to ensure consistency, comparability and reproducibility. If confirmed, SIP planning could represent a revolution in high-dose radiotherapy, opening new scenarios in treating critical disease sites not typically suitable to receive an ablative treatment.

5. Conclusions

Despite the limits of the available literature, studies that prioritize critical OAR dose constraints through SIP planning or similar dose painting strategies seem to limit severe toxicities while preserving local control in pancreatic-biliary SRT. Improvements in reporting of planning strategies (from contouring to delivery) and an ad hoc study design are essential to confirm these promising results and ensure data comparability.

Author Contributions: Conceptualization: M.L.B.; Investigation: M.L.B., G.P., M.C., E.M., G.C., L.G., N.S., V.M., F.F., P.V., F.T., L.T., D.T., M.B. and S.M.M.; Writing—original draft: M.L.B., G.P., J.B. and M.C.; Writing—review & editing: M.L.B., J.B., M.C., G.P., M.B. and S.M.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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