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Stereotactic radiotherapy in the liver hilum

Basis for future studies

Stereotactic body radiotherapy (SBRT) has developed to a promising therapeutical option [8] for metastases and small primary tumors in the lung [27, 32, 33, 36], liver [12, 13, 14, 15, 32, 33, 34, 36] or adrenal glands [9]. Some groups have started using SBRT for the treatment of tumors in the liver hilum, i.e., pancreatic cancer and distal cholangiocarcinoma (Klatskin tumors) [2, 7, 16, 20, 21, 25, 29]. To investigate further SBRT options in these challenging diseases, we decided to compare our own experience with the results of other groups. The main purpose of this review was to gain a basis for future trials and to start optimizing the clinical planning processes and dosage concepts including dose constraints for organs at risk in SBRT of the liver hilum.

Methods

A PubMed search (last search date 02 February 2011) with the key words [Stereotactic radiotherapy AND pancreas/pancreatic cancer; 25/36 hits] and [Stereotactic radiotherapy AND Klatskin tumor/cholangiocarcinoma/liver hilum; 3/10/1 hits] was performed (total: 75 hits). Second, a Medline Ovid search (last search date: 02 February 2011) with the same keywords resulted in 13 hits. The PRISMA flow diagram of search results and exclusion process is shown in **Fig. 1**. A total of 8 evaluable studies were found ([7, 16, 20, 21, 23, 25, 28, 29], **Tab. 1**). Four of them appeared to be pilot trials to test SBRT as a new treatment option, two were phase I trials, and two were phase II trials. The trials were compared with regard to SBRT concept, dose constraints, and toxicity. As the patient groups were highly heterogeneous, survival or tumor control outcome could not be compared reasonably. Although calculation models for biological effective dose or 2 Gy standard fractionation dose may lack precision in high single doses, we decided to use the linear-quadratic model to gain a possibility for comparing different dosages in the tumor as well as in the organs at risk.

Results

Two studies with a total of 40 patients with extrahepatic cholangiocarcinoma and 6 studies with a total of 244 patients with pancreatic cancer were found (**Tab. 1**). Data for the topic was rare and there was no reliable evidence for this kind of treatment. Nevertheless, the preliminary results with SFRT in the liver hilum seem to be promising. Some findings concerning toxicity were varied greatly.

Tumor control and survival

Tumor control and/or survival outcome are not primary endpoints in phase I/II or pilot trials. Therefore, these results are not reliable and are biased by several factors, e.g., additional chemotherapy or other therapies. Thus, these have to be compared cautiously. In the Freiburg pilot trial for patients with advanced stage Klatskin tumors [25], promising results were found: the median overall survival after diagnosis was 32.5 months as compared to >10 months in the Aarhus Klatskin trial [21]. In the pancreatic cancer patients the results from Stanford [7, 20], Harvard [23], Pittsburgh [29], and Italy [28] were promising as far as local tumor control was concerned, while the Aarhus results were not [16]. The median overall survival in the Aarhus/Copenhagen pancreas study was 5.4 months, the local tumor control rate after 6 months was 57% as compared to 6.4 months and about 90% in the phase II Stanford data [7]. The Har-

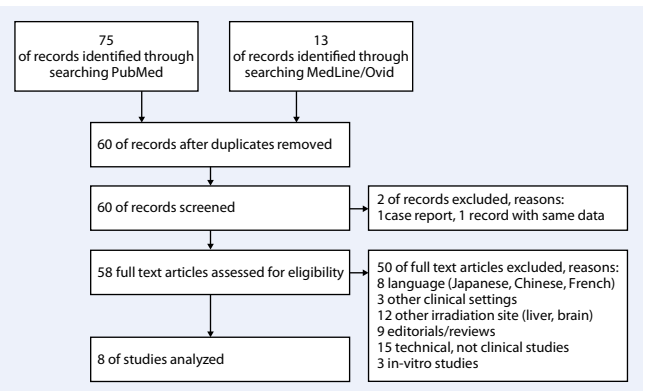

Fig. 1 ◀ PRISMA flow diagram of literature search

Tab. 1 **Patients and technique**

	Freiburg 2010 [25]	Aarhus 2010 [21]	Stanford 2004 [20]	Stanford 2009 [7]	Pittsburgh 2010 [29]	Aarhus/Cop. 2005 [16]	Harvard 2010 [23]	Italy 2010 [28]
Patients (*n*)	13	27[b]	15	77	71	22	36	23
Disease	Klatskin	Klatskin	Pankreas	Pankreas	Pankreas	Pankreas	Pankreas	Pankreas
Trial	Pilot	Pilot	Phase I	Phase II	Pilot	Phase II	Pilot	Phase I
Machine	LINAC	LINAC	CyberKnife®	CyberKnife®	CyberKnife® /LINAC	LINAC	CyberKnife®	CyberKnife®
Gating	No	No	Yes	Yes	Yes	No	Yes	Yes
IGRT	4/13 patients	No	Yes	Yes	Yes	No	Yes	Yes
Dosage concept	95% isodose PTV	67% isodose PTV 95% isodose CTV	Isodose covering 95% of PTV	Isodose covering 95% of PTV	80% isodose PTV	67% isodose PTV 95% isodose CTV	Isodose covering 95% of PTV	Isodose covering 95% of PTV
Total dose (Gy)	48	45	15–25 dose escalation	25	18–25	45	24–36[d]	30
Fractions	12	3	1	1	1	3	3	3
Total dose Standard 2 Gy $\alpha/\beta = 10$ Gy	56	94	31–73	73	42–73	94	36–66	50
Total dose Standard 2 Gy $\alpha/\beta = 4$ Gy	64	142	47–121	121	66–121	142	48–96	70
PTV (cm^3)	190 (47–393)	–	–	–	–	136 (38–376)	–	
CTV (cm^3)	–	32 (9–205)	–	–	–	32 (7–102)	–	
GTV (cm^3)	n.a.	n.a.	29.0 (19.2–71.9)	Diameter: < 7.5 cm	19 (5.1–249)	Diameter: 3.8 cm (2.0–6.1)	79.2 (16–223)	187 (108–350)
Volume concept	PTV = ITV + 10 mm[a]	PTV = CTV + 5 mm/10 mm	PTV = GTV + 2–3 mm	PTV = GTV + 2–3 mm	PTV = GTV + 2 mm	PTV = CTV + 5 mm/10 mm	PTV = GTV[c]	PTV = GTV + 2–3 mm
Toxicity	Acceptable	Considerable	Acceptable	Acceptable	Acceptable	Not acceptable	Acceptable	Acceptable

[a]Patients with IGRT (cone beam CT): ITV + 5–7 mm[b]One patient with intrahepatic cholangiocarcinoma[c]5 mm margin to check for "cold areas" adjacent to tumor in the dose gradient[d]depending on relationship between duodenum and pancreatic tumor**CTV** clinical target volume, **GTV** gross tumor volume, **PTV** planning target volume, **n.a.** not applicable.

vard data [23] showed a local control rate of 78% over a 24-month follow-up. The median progression-free survival was 9.6 months.

Side effects

In the Stanford data [7, 20], a 10% rate of grade 3 or 4 toxicity was found. There were no treatment-related deaths. Most serious toxicity was a small bowel perforation requiring surgery in one patient. The 6- and 12-month rates of late grade 2 toxicity were 11% and 25%, respectively. Considering the risk of local failure in patients with advanced pancreatic cancer, this data seem to be acceptable. In the Harvard data, 3 cases (8%) of acute grade 3 toxicity occurred [23]. Late toxicity occurred in 2 patients requiring transfusion for gastrointestinal bleeding. No patient from the Italian study [28] showed acute or late gastrointestinal toxicity > grade 1. In contrast, 2 weeks after radiotherapy 100% of the Aarhus patients suffered from grade 2 nausea [16]. In further follow-up [16], 2 patients had serious mucositis, 2 patients had stomach/bowel ulcerations, and 1 patient had a perforation of a stomach ulcer. As the median overall survival in these patients was 5.4 months and most side effects in the Stanford patients occurred more than 6 months after therapy [7], one has to take into account that some of the patients did not survive long enough for toxicity to be recorded. Six patients from the Aarhus Klatskin tumor study had severe gastrointestinal ulcerations, while 3 had duodenal stenosis [21]. In total, toxicity in the Aarhus trials is reported as not acceptable, whereas the other groups found comparatively mild side effects (**Tab. 1**). Fractionated SBRT as in the Freiburg trial [25] was well tolerated (mild nausea and vomiting).

Dosage concepts and dose constraints

One important point causing differences in toxicity of SBRT are dosage concepts (**Tab. 1, 2**). In SBRT, doses are frequently calculated for the 60% or 80% isodose line surrounding the planning target volume (PTV) causing an overdosage in the middle of the PTV. This system originates from the roots of stereotactic irradiation in neuro-oncology and is highly valuable for the irradiation of small tumors in the lung or the liver. In the liver hilum, the situation appears to be completely different: the PTV contains considerable volumes of organs at risk, e.g., the duodenum. A ho-

Abstract · Zusammenfassung

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Stereotactic radiotherapy in the liver hilum. Basis for future studies

Abstract

Background. A basis for future trials with stereotactic body radiotherapy (SBRT) for tumors of the liver hilum should be established. Thus, dosage concepts, planning processes, and dose constraints as well as technical innovations are summarized in this contribution.

Methods. On the background of our own data, the current literature was reviewed. The use of SBRT in the most common tumors of the liver hilum (pancreatic cancer and Klatskin tumors) was investigated. Dose constraints were calculated in 2 Gy standard fractionation doses.

Results. A total of 8 pilot or phase I/II studies about SBRT in the liver hilum were identified. In recent years, the SBRT technique has developed very quickly from classical stereotactic body frame radiotherapy to IGRT techniques including gating and tracking systems. In the studies using classical body frame technique, patients experienced considerable toxicities (duodenal ulcer/perforation) as compared to tolerable side effects in IGRT studies (<10% grade 3 and 4 toxicities). Dose constraints for duodenum, liver, kidneys, colon, and spinal cord were derived from the investigated studies. Survival and local tumor control data are very heterogeneous: median survival in these patients with locally advanced pancreatic or Klatskin tumors ranges between 5 and 32 months. Excellent local tumor control rates of about 80% over 24 months were achieved using SBRT.

Conclusion. Despite a few negative results, SBRT seems to be a promising technique in the treatment of tumors of the liver hilum. Highest precision in diagnostics, positioning, and irradiation as well as strict dose constraints should be applied to keep target volumes as small as possible and side effects tolerable.

Keywords

Stereotactic body radiotherapy · Liver hilum · Pancreatic cancer · Cholangiocellular carcinoma

Stereotaktische Strahlentherapie in der Leberpforte. Grundlagen für zukünftige Studien

Zusammenfassung

Hintergrund. Es sollte eine Basis für zukünftige Studien mit Körperstammstereotaxie (SBRT) im Bereich der Leberpforte gelegt werden. Hierfür wurden Dosierungskonzepte, Planungsprozesse und Grenzdosen sowie technische Innovationen betrachtet.

Methoden. Vor dem Hintergrund eigener Daten wurde die aktuelle Literatur zusammengefasst. Die SBRT wurde bei den gängigsten Tumoren der Leberpforte (Pankreaskarzinom und Klatskin-Tumor) untersucht. Grenzdosen wurden für eine 2-Gy-Standardfraktionierung errechnet.

Ergebnisse. Insgesamt wurden 8 Pilot- oder Phase-I/II-Studien über SBRT in der Leberpforte gefunden. In den letzten Jahren hat sich die SBRT sehr schnell von der klassischen Körperstammstrahlentherapie im stereotaktischen Rahmen zur bildgeführten Strahlentherapie (IGRT), einschließlich der Gating- und Tracking-Systeme, weiterentwickelt. Die Patienten in den Studien mit der klassischen Technik erfuhren erhebliche (Ulcera/Perforationen des Duodenums), die in den IGRT-Studien tolerable Nebenwirkungen (Toxizitätsrate Grad 3 und 4 < 10%). Grenzdosen für Duodenum, Leber, Nieren, Kolon und Rückenmark konnten den untersuchten Studien entnommen werden. Die Daten für das Überleben und die lokale Tumorkontrolle sind sehr heterogen: Das mediane Überleben dieser Patienten mit weit fortgeschrittenen Pankreaskarzinomen oder Klatskin-Tumoren betrug zwischen 5 und 32 Monaten. Exzellente Raten für die lokale Tumorkontrolle von etwa 80% über 24 Monate waren mit der SBRT erreichbar.

Zusammenfassung. Trotz einiger negativer Ergebnisse scheint die SBRT eine vielversprechende Technik bei der Behandlung von Tumoren der Leberpforte zu sein. Höchste Präzision bei Diagnostik, Positionierung und Bestrahlung sowie strenge Grenzdosen müssen eingehalten werden, um Zielvolumina möglichst klein und die Nebenwirkungen tolerabel zu halten.

Schlüsselwörter

Stereotaktische Körperstammstrahlentherapie · Leberpforte · Pankreaskarzinom · Cholangiozelluläres Karzinom

mogeneous dose distribution of 95–107% allows treatment of such structures with care and to omit side effects. The 4 Gy single doses used in the Freiburg study are a compromise between tumor and organ at risk biology and the technical efforts necessary for every single treatment fraction.

According to our own experience and to the review results, we would propose strictly adhering to the following dose constraints.

Duodenum

This is the most sensible organ at risk in SBRT of the liver hilum. If the whole circumference is not included in the target volume, the duodenum seems to tolerate comparatively high radiation doses. In the Stanford data (**Tab. 2**) with a single dose, the 12.5 Gy isodose line should not reach the nonadjacent duodenal wall. In addition, 22.5 Gy should not be given to more than 5% and 12.5 Gy to more than 50%, respectively. In our data, the maximum dose of 48 Gy in 12 fractions should not be given to more than 25% of the duodenal circumference. Both groups reported tolerable toxicity. Calculated for 2 Gy/fraction standard dose with an α/β of 4 Gy, this meant a maximum dose of 99.4 Gy for 5% of the duodenal volume and 34.4 Gy to the whole circumference or 64 Gy to less than 25% of the circumference. The Aarhus group [21] showed a relationship between the irradiated duodenal volume at different doses of more than 24 Gy in three fractions (48 Gy with 2 Gy standard fractionation) and the occurrence of duodenal stenosis and duodenal toxicity ≥ grade 2.

Tab. 2 **Dose constraints**

	Freiburg [25]	Aarhus [21][a]	Stanford [7, 20][b]	Pittsburgh [29]	Harvard [23]
Total dose (Gy)	**48**	**45**	**15–25**	**18–25**	**24–36**
Fractions (*n*)	**12**	**3**	**1**	**1**	**3**
Duodenum α/β = 4 Gy	48 Gy to max. 25% of circumference	As low as possible	22.5 Gy to max. 5% 12.5 Gy to max. 50% 12.5 Gy isodose should not reach the nonadjacent wall of lumen	15.1 Gy (7.7–21.6 Gy)	1/3 of circumference or more < 24 Gy < 1/3 of circumference < 30 Gy
Max. dose/fraction	4 Gy	–	22.5 Gy	21.6 Gy	10 Gy
Max. standard dose 2 Gy	64 Gy to max. 25%	–	99.4 Gy	92.2 Gy	70 Gy
Liver α/β = 1 Gy	< 40 Gy to 50%	33% < 12 Gy	< 5 Gy to 50% < 2.5 Gy to 70%	8.4 Gy (3.7–19.5 Gy)	< 30% ≥ 21 Gy < 50% ≥ 15 Gy
Max. dose/fraction	3.33	4	5	19.5	–
Max. standard dose 2 Gy	57.7 Gy to 50%	20 Gy to 33%	10 Gy to 50%	133.3 Gy max. dose	56 Gy to < 30%
Kidneys α/β = 2 Gy	< 15 Gy to 75%	50% each < 12 Gy	< 5 Gy to 75% each	Right: 2.9 Gy (0.52–11.4 Gy) Left: 3.5 Gy (0.7–13.3 Gy)	Each kidney < 25% ≥ 12 Gy
Max. dose/fraction	1.25 Gy	4 Gy	5 Gy	13.3 Gy	–
Max. standard dose 2 Gy	12.2 Gy to 75%	18 Gy to 50%	8.75 Gy to 75%	50.9 Gy max. dose	18 Gy to < 25%
Colon α/β = 5 Gy	48 Gy	As low as possible	21 Gy max.	–	30 Gy
Max. dose/fraction	4 Gy	–	21 Gy	–	10 Gy
Max. standard dose 2 Gy	61.7 Gy max.	–	78 Gy max.	–	64.3 Gy
Spinal cord α/β = 2 Gy	36 Gy max.	Max. < 18 Gy	5 Gy max.	1.8 Gy (1.03–6.9 Gy)	12 Gy max.
Max. dose/fraction	3 Gy	6 Gy	5 Gy	6.9 Gy	4 Gy
Max. standard dose 2 Gy	45 Gy max.	49.5 Gy max.	8.75 Gy max.	15.3 Gy max.	18 Gy max.

[a]Pancreas trial Aarhus/Copenhagen: no dose constraints given[b]Italian study [28] used the same dose constraints**Max.** maximum

Thus, it is important not to irradiate the complete duodenal circumference with doses higher than the calculated 35 Gy in 2 Gy standard fractionation. For small volumes < 5%, the duodenum can tolerate doses up to a calculated 100 Gy in 2 Gy standard fractionation. Finally, 25% of the duodenal circumference should be irradiated with no more than calculated 64 Gy in 2 Gy standard fractionation.

Recently, Murphy et al. [26] published for the first time a dosimetric model of duodenal toxicity after SBRT for pancreatic cancer. They found most duodenal toxicity appearing in a time span from about 5–12 months after SBRT. Furthermore, they report significant cut off volumes for an increased risk of duodenal toxicity grade 2–4 if receiving doses of 10, 15, 20, or 25 Gy. The easiest way to predict duodenal toxicity ≥ grade 2 was to look at the maximum dose to 1 cm^3 of duodenum: almost 50% of the patients receiving a maximum single dose ≥ 23 Gy experienced toxicity ≥ grade 2 as compared to about 10% of patients receiving < 23 Gy.

Liver

Our own concept allowed a high dose of up to 40 Gy to 50% of the liver. This limit (58 Gy in 2 Gy standard fractionation) was not reached in any of the patients (**Tab. 2**). The other groups were much more conservative: 5 Gy single dose to 50% (10 Gy in 2 Gy standard fractionation) was the maximum given at Stanford. The Pittsburgh group just gave maximum doses, which were not related to partial volumes of the liver and, thus, not comparable to other results. In addition, the 20 Gy in 2 Gy standard fractionation given by the Aarhus group did not lead to any serious liver toxicity.

In their summarizing review for SBRT in different regions, Chang and Timmerman [8] gave the critical volume for the liver with 700 cm^3 which should be irradiated with a maximum of 17.1 Gy in 3 fractions or 21 Gy in 5 fractions. This corresponds to 2 Gy standard fractionation doses of 38.2 and 36.4 Gy, respectively.

Kidneys

Given in 2 Gy standard fractionation, the dose constraints were 8.75–12 Gy to 75% of both kidneys or up to 18 Gy to 50% of both kidneys (**Tab. 2**). No relevant kid-

Tab. 3 **Suggested dose constraints for SBRT in the liver hilum**

	Dose constraint in 2 Gy standard fractionation
Duodenum α/β = 4 Gy	– 64 Gy to max. 25% of circumference – 100 Gy dose maximum in < 5% – 35 Gy to 50% – 35 Gy max. to nonadjacent duodenal wall
Liver α/β = 1 Gy	– 20 Gy to 33% – 10 Gy to 50% – 700 cm^3 max. 36 Gy
Kidneys α/β = 2 Gy	Kidney volume taking into account split renal function – 10 Gy to 75% (both kidneys) – 18 Gy to 50% (both kidneys)
Colon α/β = 5 Gy	– 62 Gy max. dose – 45 Gy max. on complete circumference
Spinal cord α/β = 2 Gy	– 45 Gy max. dose

ney toxicity was reported. In practice, it was of high value to measure the split kidney function. In most cases of SBRT to the liver hilum, the left kidney was shielded better than the right kidney.

Colon

The colon maximum dose was given in two of the studies investigated (**Tab. 2**). The 2 Gy standard fractionation maximum doses were 61.7 Gy and 78 Gy. It was not allowed to give such a high maximum dose to the whole circumference of the organ.

Spinal cord

The studies with SBRT single doses had very strict dose constraints of 8.75–15.3 Gy in 2 Gy standard fractionation (**Tab. 2**). The other studies had calculated the usual dose limits for fractionated radiotherapy with 45 and 49.5 Gy (2 Gy standard fractionation).

Discussion

Diverging results are reported in the literature by various groups for SBRT in the liver hilum. In contrast to the Aarhus group, the other studies reported promising results for local tumor control and an acceptable toxicity. The Aarhus group performed classical stereotactic body radiotherapy. They did not use image guiding or gating/tracking of implanted fiducials. Therefore, they had to use relatively wide safety margins and large planning target volumes. Furthermore, in this group very high irradiation doses were used: 45 Gy in three fractions on the CTV match a standard dose in 2 Gy fractions of 142 Gy if an α/β value of 4 Gy for the duodenum is assumed. In addition, in both Aarhus studies no clear dose constraints for the duodenum and the stomach were given and no dose escalation trial had been performed. Due to all these reasons, it could be expected that unacceptable toxicities were mainly found in the duodenum. Nevertheless, these negative results are very valuable to point out the necessity of extensive efforts in the further development of high precision radiotherapy in challenging abdominal regions.

Our own data [25] differ from the other studies by the comparatively low single doses used. In this dosage concept, a compromise was made between the complex technique and positive fractionation effects. Treatment with 12 fractions means a 12-fold effort in irradiation delivery as compared to the single-dose treatment. With fractionation, one of the largest advantages of high precision radiotherapy is foregone, the biologically extremely valuable high single dose. On the other hand, this concept allows for radiotherapy in challenging areas: sensible tissues can be preserved by shrinking the treatment volume and exploiting the fractionation effect. In the near future, further simplification of positioning and image guiding as well as fast treatment techniques as VMAT will offer even better possibilities to shorten positioning and treatment time and, thus, allow for fractionation.

Technology

After starting SBRT in the 1990s using a classical body frame technique [3, 13, 22, 37], the method was continuously refined [5, 6, 10, 11]. The most important developments were possibilities for image guiding and improved positioning equipment [18]. Positioning control by cone beam CT scans before every single fraction allow PTV safety margins to be reduced and, thus, better preservation of organs at risk [17]. The Cyber Knife® technique with implanted fiducials used at the US and Italian centers also uses gating and tracking systems, which result in better results. Thus, in SBRT of the liver hilum, technology is important.

Another important point is the diagnostic imaging for treatment planning. SBRT can only be as precise as the tumor's picture is. Information of high resolution MRI and CT scans is recommended for SBRT planning. In this context, 4D imaging including PET or PET/CT may play an increasing role [24].

Endpoints for future studies

In future SBRT studies, the endpoints will have to be fixed with high accuracy: in addition to survival, local tumor control will be of importance. In some of the reported retrospective trials, the diagnostic methods for follow-up were not clearly defined. Local tumor control should be measured by MRI or CT scans (e.g., the Havard data had clearly defined contrast-enhanced CT scans). In this context, PET techniques may be of increasing importance [30]. Follow-up imaging might develop similarly to stereotactic radiotherapy in neuro-oncology [1]. In addition, imaging tumor markers may be a valuable endpoint as was shown by Ca 19–9 measurements in the Harvard data [23].

Finally, in patients treated by SFRT, quality of life (QoL) should also be investigated. In these vulnerable, palliative patients, instruments for measuring individual QoL should be established. QoL may become an important argument for the use of SBRT if compared to extensive surgical procedures [35].

Combination with chemotherapy and surgery

An important advantage of SBRT is the short time required for this therapy. Patients treated with SBRT can be given full dose chemotherapy much earlier than patients treated by conventionally fractionated irradiation. As pancreatic cancer patients tend to suffer from early systemic disease (liver metastases or peritoneal carcinosis), this may be important. In treatment of tumors in the liver hilum, SBRT (± sequential chemotherapy) will have to be compared with combined radiochemotherapy schedules including conventionally fractionated IMRT [4].

In the Italian study [28], SBRT was used together with gemcitabine chemotherapy in a potentially neoadjuvant treatment concept: 6 of 23 patients (26.1%) had a resectable pancreatic tumor after chemotherapy and SBRT. Two were operated, 2 patients refused resection, and 2 were not operated due to systemic disease.

SBRT boost after radiochemotherapy

In one prospective [19] and one retrospective [31] study (19 and 30 patients, respectively), SBRT was investigated as a boost in the context of a conventionally dosed radiochemotherapy. In the retrospective data, a SBRT boost provided a safe option of increasing radiation dose. In the prospective trial, the radiochemotherapy plus SBRT boost resulted in excellent local control, but did not improve overall survival and was associated with more toxicity than SBRT alone.

Conclusion

The dose given to a PTV in the liver hilum should be calculated homogenously to the 95% isodose, because relevant organs at risk (duodenum, kidneys) cannot be shielded sufficiently without compromising tumor treatment. Overdosages like in stereotactic radiotherapy of brain, lung, or liver metastases are not tolerable.

Dose constraints suggested for SBRT in the liver hilum are summarized in Tab. 3.

In radiotherapy of pancreatic carcinoma or Klatskin tumors, precise patient positioning and minimizing target volumes are important; thus, technical improvements in these areas are necessary. To face this challenging situation of tumor treatment, precise diagnostic imaging as well as IGRT techniques including tracking and gating should be used whenever possible.

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Conflict of interest. The corresponding author states that there are no conflicts of interest.

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