Stereotactic Radiotherapy of Targets in the Lung and Liver

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Background: Stereotactic irradiation of extracranial targets offers a non-invasive treatment modality for patients with localized tumors, which are not amenable for surgery or other invasive approaches because of age or impaired medical condition. The purpose of the study was the evaluation of the method to achieve local control of irradiated targets in relation to treatment toxicity.
Patients and Methods: Irradiation was performed as hypofractionated treatment in three fractions of 10 Gy each, normalized to the PTV enclosing 65% isodose with patient fixation in a stereotactic body frame. The isocenter was localized by stereotactic coordinates. Targets were circumscribed tumors in the lung (n = 27) and liver (n = 24) not amenable for other treatment modalities: primary lung cancer (n = 12), local recurrences of lung cancer (n = 4), lung metastases (n = 11), liver metastases (n = 23) and one cholangiocellular carcinoma. Median CTV/PTV for targets in the lung was 57/113 cm^3 (min/max 5–277 cm^3/17–343 cm^3) and for targets in the liver 50/102 cm^3 (min/max 9–516 cm^3/42–772 cm^3). Median follow-up for targets in the lung was 8 months (2–33) and 9 months (2–28) for liver targets. Local control was defined as complete or partial remission and stable disease, measured by repeated CT scans after 6 weeks and in 3 months intervals. Treatment toxicity was evaluated according to the WHO score.
Results: Crude local control was 85% for pulmonary targets and 83% for hepatic targets. Actuarial local control after 1 and 2 years was 76% and 76% for lung tumors and 76% and 61% for liver tumors. Actuarial overall patient survival was 48% after 1 year and 21% after 2 years for targets in the lung and 71% and 43% for targets in the liver. No acute grade 3–5 side effects were observed. Serious late toxicity occurred in two patients: a chronic ulceration of the esophagus at a target close to the mediastinum after 3 months (grade 3) and fatal bleeding from the pulmonary artery after 9 months (grade 5) in a previously irradiated patient. It remained unclear, whether the bleeding was a side effect of irradiation or due to tumor infiltration.
Conclusion: Hypofractionated stereotactic irradiation of targets in the lung and liver is a locally effective treatment with actuarial local control rates of 76% after 1 year and 61–76% after 2 years without relevant acute toxicity. Severe late toxicity did not occur, if targets close to the mediastinum were avoided.

Key Words: Stereotactic radiotherapy · Body radiosurgery · Stereotactic body frame · Conformal radiotherapy · Hypofractionated radiotherapy · Lung tumors · Liver metastases

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Stereotaktische Strahlentherapie von Tumoren in der Lunge und Leber

Hintergrund: Prüfung eines hypofraktionierten, stereotaktischen Behandlungsansatzes für Bestrahlung lokalisierter Raumforderungen in der Lunge und Leber hinsichtlich lokaler Tumorkontrolle und Nebenwirkungen.
Patienten und Methode: Stereotaktische Bestrahlung in drei Fraktionen à 10 Gy, normalisiert auf die PTV-umschließende 65%-Isodose mit Patientenfixierung im stereotaktischen Körperrahmen. Insgesamt wurden 27 Lungentumoren (zwölf primäre und vier lokoregionär rezidivierte Bronchialkarzinome, elf Metastasen) und 24 Lebertumoren (23 Metastasen, ein cholangiozelluläres Karzinom) behandelt. Das CTV/PTV für Lungenherde betrug im Median 57/113 cm^3 (min/max 5–277 cm^3/17–343 cm^3), für Leberherde 50/102 cm^3 (min/max 9–516 cm^3/42–772 cm^3). Die mediane Nachbeobachtungszeit betrug 8 Monate (2–33) für Lungen- und 9 Monate (2–28) für Leberherde. Lokale Kontrolle wurde definiert als computertomographisch komplette oder partielle Remission sowie Wachstumsstopp 6 Wochen sowie in Intervallen von 3 Monaten nach Therapie. Die Nebenwirkungen wurden nach WHO klassifiziert.
Ergebnis: Lokale Kontrolle betrug numerisch in der Lunge 85%, in der Leber 83%, aktuarisch in der Lunge 76% nach 1 und 2 Jahren, in der Leber 76% nach 1 Jahr, 61% nach 2 Jahren. Das aktuarische Gesamtüberleben lag nach 1 und 2 Jahren bei Lungenherden bei 48% und 21% bzw. bei Leberherden bei 71% und 43%. Akut traten keine Nebenwirkungen Grad 3–5 auf. Als Spätnebenwirkung wurden eine chronische Ösophagitis (Grad 3) bei einem dicht am Mediastinum gelegenen Tumor sowie eine fatale Blutung aus der Arteria pulmonalis beobachtet, bei der jedoch auch eine tumorbedingte Arrosionsblutung nicht auszuschließen war.

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Schlussfolgerung: Die stereotaktische Bestrahlung von Lungen- und Leberherden ist eine effektive Behandlungsform mit aktuarischen lokalen Kontrollraten bis zu 76% nach 1 Jahr bzw. 61–76% nach 2 Jahren. Die Akuttoxizität war gering; schwere Spätnebenwirkungen traten nicht auf, wenn Zielvolumina in der Nähe des Mediastinums vermieden wurden.

Schlüsselwörter: Stereotaktische Bestrahlung · Körperstereotaxie · Stereotaktischer Körperrahmen · Konformale Strahlentherapie · Hypofraktionierte Strahlentherapie · Lungentumoren · Lebermetastasen

Introduction

Stereotactic irradiation is an effective treatment of brain tumors and cerebral metastases. Large single doses can be delivered precisely to small, well circumscribed lesions. According to this experience and the increasing availability and usage of 3-D-conformal treatment techniques stereotactic irradiation was introduced to achieve local control of extracranial tumors or metastases. The non-invasive concept of stereotactic irradiation offers a treatment modality even for medically impaired patients, who are not amenable for surgery or general anesthesia.

For extracranial stereotactic radiotherapy different indications for treatment and different concepts of dose and dose prescription have been reported: Blomgren et al [2, 3] treated a wide spectrum of circumscribed lesions such as small lung tumors, pulmonary metastases, liver tumors, abdominal metastases or tumor recurrences and bone metastases, Nakagawa et al [13] and Uematsu et al [18] irradiated small lung tumors only. Herfarth et al [6, 8] treated lesions in the lung and liver. Dose and fractionation ranged from single dose irradiation with 12–24 Gy/isocenter [6, 8, 13] to hypofractionated treatment with 2–4 fractions of 10–15 Gy/PTV enclosing 65%-isodose [2, 3, 9–11, 20] and 5–15 fractions with a total of 30–75 Gy/tumor enclosing 80%-isodose [18]. Special immobilization devices have been constructed and are commercially available for stereotactic treatment of extracranial targets. These devices reduce setup uncertainties and target mobility and increase reproducibility of the target to keep the irradiated volume as small as possible. Although many institutions have started to treat patients with extracranial stereotactic radiotherapy, very few clinical results have been published.

In our clinic stereotactic irradiation of extracranial targets is performed since November 1997. Until April 2001 26 patients with 27 lesions in the thorax and 21 patients with 24 lesions in the liver were treated by stereotactic irradiation with 3×10 Gy/65%-isodose. The purpose of the study was to evaluate the role of the stereotactic approach to achieve local control compared to treatment toxicity. In this report we present the clinical results in terms of local tumor control, overall survival and side effects.

Patients and Methods

The concept of stereotactic irradiation of extracranial targets at our institution was based on the method described by Blomgren and Lax from Karolinska Hospital, Stockholm [2, 3, 9–11]. Compared to conformal radiotherapy the method is a stereotactical approach because the isocenter definition and localization is performed by stereotactic coordinates alone (no skin marker), high fraction doses are aimed to induce tumor necrosis and an inhomogeneous dose distribution is used as it is common practice in stereotactic radiotherapy.

For patient immobilization and stereotactic setup a Stereotactic Body Frame (SBF) was used, which was introduced by Lax and Blomgren and is commercially available from Elekta Oncology Systems. The SBF is constructed not only as an immobilization device, but additionally represents an external reference system, which is used to locate the isocenter and target position by stereotactic coordinates instead of skin markers or bony reference structures. The reference system allows direct identification of the stereotactic coordinates in each CT slice and in the 3-D-treatment planning system. In the SBF the patient is immobilized in an individualized vacuum pillow. For repeated patient positioning two laser systems at the trunk and the legs are attached to the SBF. Additionally a diaphragm control device can be used to reduce breathing mobility of targets in the lower lung and liver by pressing a pentagonal template in the patient's epigastrium. Technical details of the SBF, the procedure of patient positioning and repositioning at our institution and results of treatment accuracy related to different types of targets have been described previously [20].

Patient and Target Selection

Each patient was informed about the new approach of stereotactic radiotherapy to extracranial targets and the role of the established treatment options such as surgery, chemotherapy or normofractionated radiotherapy. The rationale for considering stereotactic treatment was that standard treatment options were not feasible for different reasons in the majority of cases or the patient himself refused the standard treatment as surgery or chemotherapy. Only with informed consent of the patient stereotactic irradiation was performed.

Patient selection followed three general criteria:

1. There should be a potential benefit from stereotactic treatment due to an increased dose to a small volume compared to conventional radiotherapy, resulting in an increased probability of local control with decreased treatment related side effects.
2. Local control should be beneficial for the patient's quality of life or prognosis.
3. There should be no other superior treatment modality available, e.g. the patient or the tumor should be considered as

inoperable or not amenable for other invasive or non-invasive treatment.

Objective criteria for patient selection were Karnofsky performance status of ≥ 70 and a sufficient pulmonary (FEV1 > 1 l/s, VC > 3l) and liver (no icterus, no ascites, normal blood coagulation) function. Generally the target volume (expected PTV) is related to the lung and liver function (impaired function – small target). The volume of the 5-Gy isodose was not to exceed 50% and the 7-Gy isodose not to exceed 30% of the functional organ tissue. Organs at risk as bronchi, trachea, heart, stomach, duodenum and small or large bowel were kept out of the 7-Gy isodose to avoid serious side effects. Due to the lack of clinical data on the effect of very high fraction doses exceeding 8 Gy, the dose of 7 Gy was chosen based on the experience in brachytherapy, where 7 Gy to a small volume (5 cm^3) of an organ at risk are tolerated [14].

For stereotactic irradiation in the thorax cavity medically inoperable non-small-cell lung cancer (cT1–cT3 cN0 cM0), metastasized NSLSC, which caused local symptoms or were impending to develop local symptoms from the primary tumor, local recurrences of lung cancer with or without previous radiotherapy, intrapulmonary lung metastases (e.g. after pneumonectomy) and painful metastases (n = 2) adjacent to the thoracic wall were chosen for treatment. Three of these patients had increasing dyspnea because of progressive tumor compression of lobar bronchi. Targets in the liver were solitary metastases (n = 23) of different primaries and an inoperable cholangiocellular carcinoma. The liver metastases were either not amenable for surgery or recurrences after previous resection. Another indication were liver and lung metastases, which recurred or progressed during or after chemotherapy. A detailed description of the targets is shown in Table 1.

Patient Characteristics

From November 1997 to April 2001 27 targets in the lung and 24 targets in the liver were treated. Patient characteristics as

Table 1. Characteristics of targets in the lung and liver. Pulmonary targets are distinguished into primary lung tumors, locoregional recurrences and metastases. Additionally the whole group is divided into different target locations in the thorax. 23 of 24 hepatic targets were metastases of various histology. P: primary stereotactic irradiation; B: stereotactic boost irradiation.

Tabelle 1. Charakteristika der Zielvolumina in der Lunge und Leber. Pulmonale Zielvolumina sind unterschieden in primäre Bronchialkarzinome, lokoregionäre Rezidive und Lungenmetastasen. Zusätzlich ist diese Gruppe erneut hinsichtlich ihrer Lokalisation im Thorax beschrieben. 23 der 24 Zielvolumina in der Leber waren Metastasen unterschiedlicher Primärtumoren. P: primär stereotaktische Bestrahlung; B: stereotaktische Boost-Bestrahlung.

	No. of targets	Histology of primary tumor (number of targets)	Tumor manifestation outside the irradiated volume (%)	Fraction/dose (Gy) (norm. to the PTV enclosing 65%-isodose)
Thorax	**(n = 27)**		14/27 (52%)	
Primary lung cancer	12	Squamous cell carcinoma (3), adenocarcinoma (9)	4/12 (25%)	3 × 10 (n = 11; P) 2 × 7 (n = 1; B)
Local recurrence of lung cancer	4	Squamous cell carcinoma (3), small-cell lung cancer (1)	2/4 (50%)	3 × 10 (n = 3; P) 4 × 7 (n = 1; P)
Pulmonal metastases	11	Squamous cell lung carcinoma (4), adenocarcinoma lung (1), rectal carcinoma (2), kidney carcinoma (1), malignant thymoma (1), malignant neurinoma (1), follicular thyroid carcinoma (1)	8/11 (73%)	3 × 10 (n = 10; P) 4 × 7 (n = 1; P; target close to mediastinum)
Intrapulmonary targets	14			3 × 10 Gy (n = 13; P); 2 × 7 Gy (n = 1; B)
Intrapulmonary metastases after pneumonectomy	3			3 × 10 Gy (n = 3; P)
Central/mediastinal targets	5			3 × 10 Gy (n = 3; P), 4 × 7 Gy (n = 2; P)
Thoracic wall targets	5			3 × 10 Gy (n = 5; P)
Liver	**(n = 24)**		12/24 (50%)	
Primary liver tumor	1	Cholangiocellular carcinoma		3 × 10 (P)
Liver metastases	23	Colorectal carcinoma (11), ovarian carcinoma (4), breast carcinoma (6), kidney carcinoma (1), pancreatic carcinoma (1)	12/23 (52%)	3 × 10 (n = 21; P) 4 × 7 Gy (n = 1; P, target close to esophagus)

age, gender, performance status and general treatment parameters as treatment intention, fractionation and treated volume are shown in Table 2. Median follow-up of targets in the lung was 8 months, mean 11 months (2–33 months) and 9 months (mean 9 months, 2–28 months) for targets in the liver. In seven of 27 targets in the lung and in eleven of 24 targets in the liver chemotherapy was administered within 3 months of irradiation. The majority of these targets (five of seven in the lung and seven of eleven in the liver) were stereotactically irradiated because of residual tumor or tumor progression during or after chemotherapy. Two patients with two pulmonary targets and three patients with four hepatic targets received chemotherapy within 3 months after stereotactic irradiation.

Treatment Concept, Dose and Dose Prescription

The fraction dose of 10 Gy and its normalization to the PTV enclosing 65%-isodose followed the experience of Blomgren and Lax, who demonstrated that normalizing to the 65%-isodose leads to a 50% increase of dose in the target center without substantial increase of dose outside the PTV in comparison to dose loads for a homogenous dose distribution [9]. Because of the lack of personal experience we decided to adopt to this concept with promising clinical results. The majority of targets in the lung (24/27 targets) and the liver (23/24 targets) were irradiated with three fractions of 10 Gy to the PTV enclosing 65%-isodose. Dose, fractionation and target definition for patients with curative or palliative treatment intention were identical due to the approach of Blomgren et al [2, 3]. Nevertheless in two cases of targets in the lung and one case of a liver metastasis the dose per fraction was decreased to 7 Gy/65%-isodose because of the vicinity of the main bronchus (n = 1) or the esophagus (n = 2; one paravertebral tumor in the thorax and one liver metastasis in segment 8). To compensate for the decreased dose a fourth fraction was given in these cases. One patient with primary lung cancer received a stereotactical boost (2 × 7 Gy/65%-isodose) on the primary following conventional fractionated radiotherapy of 60 Gy/isocenter, because the tumor was located centrally in the right upper lobe and the volume of irradiated lung tissue should be decreased because of impaired pulmonary function during treatment.

Table 2. Patient and treatment characteristics for targets in the lung (26 patients with 27 targets) and liver (21 patients with 24 targets).

Tabelle 2. Patienten- und Behandlungscharakteristika der Zielvolumina in der Lunge (26 Patienten mit 27 Targets) und in der Leber (21 Patienten mit 24 Targets).

	Lung n = 27	Liver n = 24
Gender		
Male	23	7
Female	4	17
Age (years)		
Range	41–81	15–79
Median/mean	65/65	60/59
Karnofsky index prior to treatment		
Range	70–100	70–100
Median/Mean	90/87	90/91
Treatment intention		
Primary radiotherapy	24	24
Boost	1	0
Re-irradiation after previous radiotherapy	2	0
Treatment volume (cm^3)		
Clinical target volume (min/max)	5/277	9/516
CTV (median/mean)	57/72	50/99
Planning target volume (min/max)	17/343	42/772
PTV (median/mean)	113/134	102/176
Fractionation		
3 × 10 Gy/65%-isodose	24	23
2 × 7 Gy/65%-isodose boost	1	
4 × 7 Gy/65%-isodose	2	1

3-D-treatment planning was performed by the Helax TMS® versions 4.01A and 4.01B (MDS Nordion). The target was delineated as macroscopic tumor including a small margin of 2–3 mm to account for potential tumor invasion into normal tissue or the uncertainty of target visibility in the CT scan (CTV). Targets in the lung were segmented in the lung window of the CT scan, tumors in the liver depending on the largest dimension in the arterial or portal phase of a spiral CT scan with iv. contrast medium. For PTV definition a security margin of 5 mm in anterior-posterior and lateral and 10 mm in longitudinal direction was defined. In certain cases with low breathing mobility of the target and CT simulation prior to each fraction the security margin in longitudinal direction was decreased to 5 mm. The decision to decrease or increase the security margins were based on the measurement of target mobility in the planning CT. For that purpose repeated CT slices at the same target position were performed. Prior to irradiation CT simulation seemed to be important to recognize of target deviations larger than 5–10 mm, which was noticed in up to 14% [20] and was performed since August 1998 prior to each fraction.

To achieve a 3-D-conformal dose distribution usually a symmetric five-beam arrangement was individualized by addition of rotational beams or opposing beams. Usage of noncoplanar beams or extended use of wedges was avoided to shorten irradiation and immobilization time. Photon energies of 5–18 MV were used. Including CT simulation prior to treatment (ca. 20 minutes) the duration of a complete treatment session was about 60 minutes. The treatment fractions were applied in 2–4 days intervals. Patient follow-up consisted of a clinical examination 3 weeks after the last treatment session, a clinical examination plus CT scan after 6 weeks followed by CT scans in 3 months intervals. All patients were followed until death or deterioration of medical condition, so that further evaluation would not be feasible.

Treatment Evaluation

The main purpose of this trial on stereotactic irradiation of extracranial tumors was to study local control and acute and late toxicities. The majority of patients in the presented study were

treated under palliative conditions, because cure was not possible due to a metastasized disease. Nevertheless eight of twelve patients with primary irradiated lung cancer and nine of 23 liver metastases (solitary metastases of colorectal cancer) were treated under curative intention. Despite the small number of targets these subgroups have been analyzed separately, because the stereotactic approach might be a beneficial treatment option for these patients in the future. Overall survival of patients, however, was also analyzed, because patient survival should be long enough to detect local failure.

Local control was defined as stable disease, partial or complete response during the follow-up evaluated by regular CT or MRI scans. Local failure was diagnosed as tumor progression or regrowth after initial shrinking. Nevertheless a detailed categorization in complete or partial response, stable or disease or volumetry was not performed due to the difficulty to differentiate active or inactive tumor tissue from progressive fibrosis in pulmonary targets or enhancement of contrast medium as active tumor versus resorption zones in hepatic targets. For analysis of the site of local failure tumor progression at the margin of the target was distinguished from tumor progression centrally in the target.

Treatment related toxicity and symptom relief were evaluated by asking for the patients complaints. Blood analyses for monitoring liver function or tumor markers were performed prior to treatment, after finishing treatment and during follow-up. Further investigations as lung function tests or endoscopy were indicated depending on clinical needs. Side effects were categorized according to the WHO score. For statistical evaluation of local control, overall survival and the influence of volume or chemotherapy on local control actuarial analysis using the Kaplan-Meier method and the log-rank test was performed. For statistical analysis the software "Statistica", version 5.1, (StatSoft®), was used [16].

Results

Local Control

Crude local control was achieved in 85% (four local failures in 27 targets) of tumors in the lung and 83% of tumors in the liver (four local failures in 24 targets). The local failures occurred after 3, 6, 7 and 11 months (pulmonary targets) and 3, 8, 9 and 17 months (hepatic targets) resulting in an actuarial local control of 76% for both locations after 12 months and 76% (lung) respectively 61% (liver) after 24 months (Figure 1). The actuarial local control after 24 months for hepatic targets decreased substantially due to one local failure after 17 months and the low number of patients at risk at this time (n = 4). Crude local control of the eight patients treated for primary lung cancer under curative intention was 88% (one local failure after 6 months). Actuarial local control after 12 and 24 months was 86% compared to 64% for the targets treated under palliative intention (p = 0.5; n.s.). Crude local control for curative treated liver metastases was 89% (one local failure after 8 months), actuarial local control was 67% after 12 and 24 months compared to 80% and 60% after 12 and 24 months in palliative treated targets (three local failures of 15 targets) (p = 0.9; n.s.).

In 3/4 (75%) of pulmonary targets and 1/4 of liver targets (25%) local failure was relevant for the patient's condition because of no simultaneous progression of disease outside the stereotactic volume. A "learning curve" [6] was not observed: in fact the first patient treated for a liver metastasis recurred locally, but the other failures occurred at the 4th, 7th and 13th of 24 targets respectively at the 10th, 11th, 13th and 21st of 27 pulmonary targets.

The analysis of the location of local failures revealed that three of four failures in the lung occurred centrally, while three of four failures in the liver occurred marginally. Three of four marginal failures occurred at targets, where an organ at risk had to be spared (esophagus, heart/lung, lung). In these cases of targets in the lung retrospectively the CTV and PTV were too small and/or the dose gradient too sharp. For the target with marginal failure in the liver no reason besides microscopic tumor invasion beyond the CTV could be detected. The analysis of CTV, PTV and chemotherapy revealed no significant influence on local control despite the median and mean

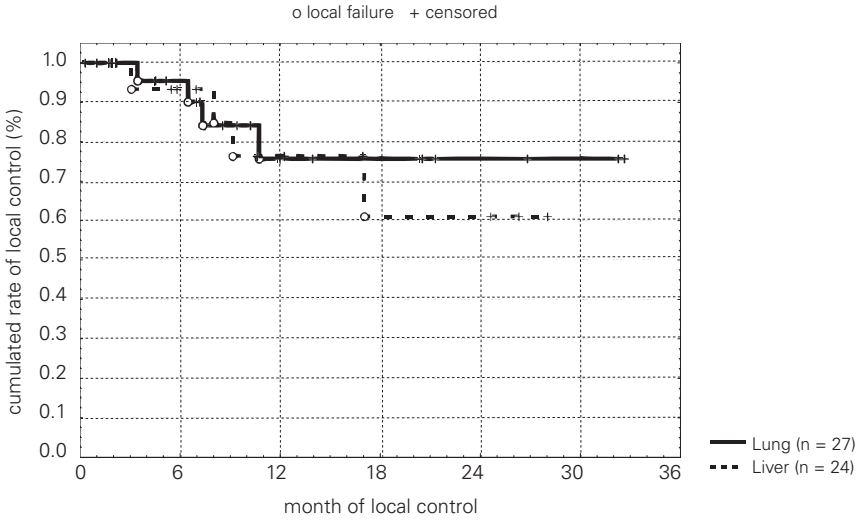

Figure 1. Kaplan-Meier analysis of local control rates for targets in the lung and liver treated by stereotactical irradiation. Local control after 12 months is 76% for both targets and 76%, respectively 61% for lung and liver targets after 24 months.

Abbildung 1. Kaplan-Meier-Analyse der lokalen Kontrolle stereotaktisch bestrahlter Zielvolumina in der Lunge und Leber. Die lokale Kontrolle betrug nach 12 Monaten 76% für beide Zielvolumina und 76% bzw. 61% nach 24 Monaten für Zielvolumina in der Lunge bzw. Leber.

CTV (79/106 cm^3) and PTV (164/187 cm^3) in locally uncontrolled targets was slightly larger than in locally controlled targets (CTV 53/85 cm^3; PTV 107/154 cm^3). Details of the characteristics of local failures are shown in Table 3. In Figures 2 and 3 CT scans of follow-up of a locally controlled target in the lung and a locally failing target in the liver are shown.

Both patients with painful thoracic wall metastases had substantial symptom relief within 6 weeks after irradiation, which persisted during follow-up (5 and 32 months). The two patients with metastasized lung cancer treated for dyspnea reported subjective symptom relief after 6 weeks. Unfortunately they simultaneously had systemic tumor progression outside the target, so that the patients died after 3 and 6 months.

Table 3. Characteristics of local failures of targets in the lung and liver. Tumorprogression: in-field recurrence; marginal progression: recurrence at the margin.

Tabelle 3. Beschreibung der Lokalrezidive nach stereotaktischer Bestrahlung von Zielvolumen in Lunge und Leber. Tumorprogression: In-Field-Rezidiv; marginal progression: Feldrandrezidiv.

Site of target	Target	Histology	Dose (Gy/65%)	CTV/PTV (cm^3)	Time to local failure (months)	Site of failure	Relevance of local failure	Patient status
Lung	Prim. tumor (lingual left lobe between heart and pleura)	Adenocarcinoma	3 × 10	82/183	6	Marginal progression at pleura and pericardium	Yes (no other tumor manifestation, no treatment option because of medical condition)	Alive 10 months after irradiation
Lung	Metastasis lung cancer (central in the left upper lobe)	Adenocarcinoma	3 × 10	45/100	11	Marginal progression to the hilus	Yes (conventional radiotherapy for treatment)	Death after 22 months due to general progression
Lung	Metastasis rectal carcinoma (close to mediastinum right, thoracic vert. 7–9)	Adenocarcinoma	4 × 7	75/145	3	Marginal progression to around the esophagus	Yes (symptomatic, pain and difficulties to swallow, chemotherapy, stent)	Death after 6 months due to progressive pulmonal metastases
Lung	Metastasis bronchial carcinoma (contralateral right upper lobe, central)	Squamous cell carcinoma	3 × 10	155/260	7	Tumor progression	No (general pulmonal progression, no further treatment)	Death after 7 months due to general progression and rapid deterioration
Liver	Metastasis kidney carcinoma	Clear-cell carcinoma	3 × 10	199/305	3	Tumor progression after initial shrinkage to 75%	No (general progression of multiple liver metastases, interferon therapy)	Death after 11 months due to progressive liver metastases
Liver	Metastasis rectal carcinoma	Adenocarcinoma	3 × 10	194/310	8	Tumor progression after initial shrinkage to 25%	Yes (no other tumor manifestation, chemo-embolization for salvage)	Alive 12 months after irradiation
Liver	Metastasis rectal carcinoma	Adenocarcinoma	3 × 10	47/107	9	Tumor progression after initial shrinkage to 50%	No (multiple other hepatic metastases, intra-arterial chemotherapy)	Death after 20 months due to hepatic progression
Liver	Metastasis ovarian carcinoma	Clear-cell carcinoma	3 × 10	47/82	17	Marginal progression after initial shrinkage to 25%	No (hepatic and pelvic metastases occurred, chemotherapy)	Alive 24 months after irradiation
Summary								
				CTV: 45–199 cm^3 mean/median 79/106 cm^3 **PTV:** 82–310 cm^3 mean/median 164/187 cm^3	3–17 months mean/median 8 months	Tumorprogression: Lung 1/4 (25%) Liver 3/4 (75%) Marginal progression: Lung 3/4 (75%) Liver 1/4 (25%)	Yes: Lung 3/4 (75%) Liver 1/4 (25%)	Alive 3/8 (37%) Death due to local failure: 0/8 (0%) Death due to syst. progression: 5/8 (63%)

Overall Survival

At the time of evaluation eleven of 27 (41%) patients with targets in the lung and 15 of 24 (63%) with targets in the liver were alive. Median survival was 9 months, mean 12 months (2–33 months) for pulmonary targets and at median 8 months, mean 10 months (2–28 months) for hepatic targets. In both groups only one local failure occurred beyond the median follow-up period.

Actuarial overall survival was 48% after 1 year and 21% after 2 years (lung) and 71% after 1 year and 43% after 2 years

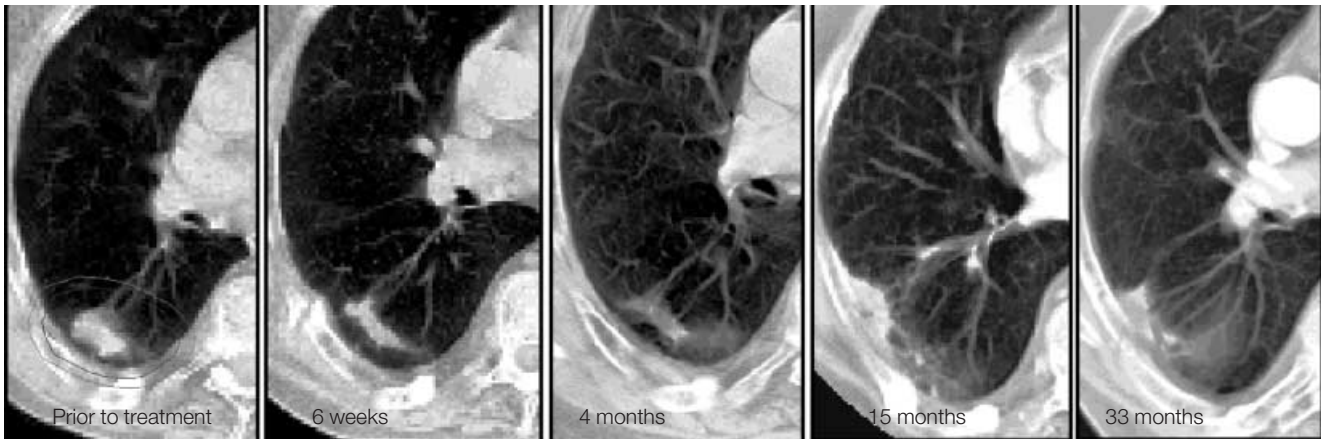

Figure 2. 62-year-old male with a medically inoperable bronchial carcinoma (squamous cell carcinoma) in the right lower lobe. Stereotactic irradiation was performed with three fractions of 10 Gy, normalized to the PTV enclosing 65%-isodose. CTV and PTV were 91 cm^3 and 174 cm^3. The CT scans during follow-up show after initial shrinkage of the tumor progressive fibrosis of the irradiated area. After 15 months a CT assisted biopsy was taken to exclude local recurrence, which revealed fibrous tissue. In the further follow-up no signs of tumor progression were observed.

Abbildung 2. Beispiel eines 62-jährigen Patienten mit medizinisch inoperablem Plattenepithelkarzinom der Lunge im rechten Unterlappen. Es wurde stereotaktisch in drei Fraktionen à 10 Gy, normalisiert auf die das PTV umschließende 65%-Isodose, bestrahlt. Das CTV und PTV betrugen 91 cm^3 bzw. 174 cm^3. Die CT-Untersuchungen zeigten nach anfänglicher Tumorverkleinerung eine zunehmende Fibrose im Bestrahlungsgebiet. Nach 15 Monaten erfolgte eine CT-gestützte Biopsie zum Ausschluss eines Rezidivs, die jedoch nur Narbengewebe erbrachte. Die weitere Nachbeobachtung zeigte keinen Hinweis auf eine Progredienz des Tumors.

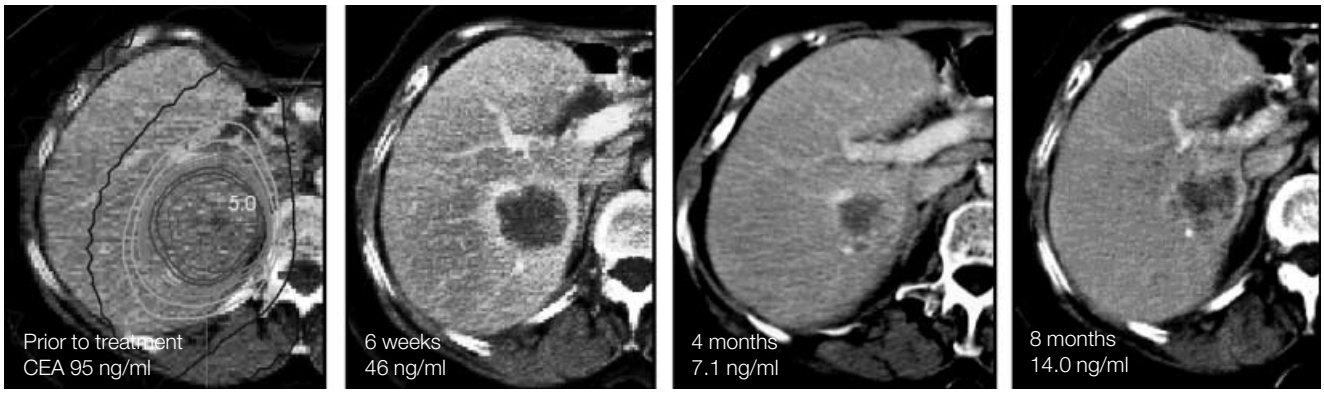

Figure 3. 66-year-old female with a metachrone solitary liver metastasis of rectal cancer, who had undergone resection of solitary metastases 1 and 2 years prior to radiotherapy. Stereotactic irradiation was performed with three fractions of 10 Gy, normalized to the PTV enclosing 65%-isodose. CTV and PTV were 194 cm^3 and 310 cm^3. The CT scans during follow-up showed after initially typical reaction of tumor necrosis with a contrast enhancing resorption zone (6 weeks) and slow tumor shrinking (4 months) a recurrence of new tumor nodules within the high-dose area after 8 months. Tumor remission and recurrence correlated to decrease and rise of CEA level.

Abbildung 3. Beispiel einer 66-jährigen Patientin mit metachroner, großer solitärer Lebermetastase eines Rektumkarzinoms, bei der bereits zweimal solitäre Metastasen 1 und 2 Jahre vor Bestrahlung reseziert wurden. Die stereotaktische Bestrahlung erfolgte in drei Fraktionen à 10 Gy, normalisiert auf die das PTV umschließende 65%-Isodose. Das CTV und PTV betrugen 194 cm^3 bzw. 310 cm^3. Die CT-Untersuchungen zeigten nach anfänglich typischem Verlauf mit Tumornekrose und Kontrastmittel aufnehmender Resorptionszone (6 Wochen) sowie langsamer Verkleinerung (4 Monate) dann nach 8 Monaten ein erneutes Rezidiv mit Tumorknoten im Hochdosisbereich. Das Tumoransprechen und -rezidiv korrelierte zu Abfall und Anstieg der CEA-Werte.

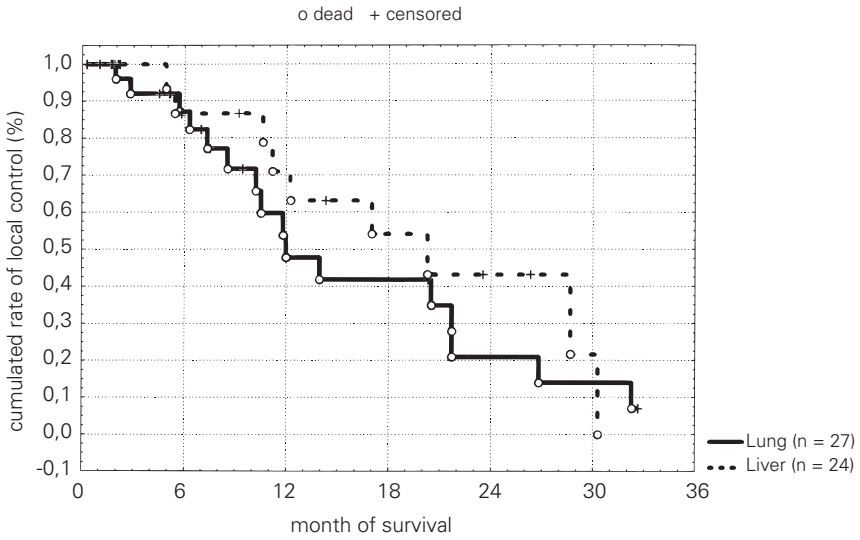

Figure 4. Kaplan-Meier analysis of overall survival of patients with targets in the lung and liver treated by stereotactical irradiation. Overall survival after 12 and 24 months was 48% and 21% for patients with pulmonary targets, respectively 71% and 43% for patients with hepatic targets.

Abbildung 4. Kaplan-Meier-Analyse des Gesamtüberlebens von Patienten mit stereotaktisch bestrahlten Zielvolumina in der Lunge und Leber. Das Gesamtüberleben betrug nach 12 und 24 Monaten 48% und 21% für Patienten mit Zielvolumina in der Lunge bzw. 71% und 43% für Patienten mit Zielvolumina in der Leber.

Table 4. Treatment toxicity according to WHO grade. Grade 1/2 was acute toxicity and occurred in lung and liver targets typically a few hours after irradiation with spontaneous remission after a few hours. In the two patients with grade 3 and 5 toxicity targets close to the mediastinum were irradiated, which now are considered as not feasible for a stereotactic approach. It remained unclear, whether the fatal bleeding from the lung was due to tumor infiltration or radionecrosis of the right pulmonary artery.

Tabelle 4. Nebenwirkungen nach WHO-Grad. Grad-1- und -2-Nebenwirkungen traten akut sowohl bei Zielvolumina in der Lunge als auch der Leber typischerweise einige Stunden nach Bestrahlung auf und sistierten spontan. Bei den beiden Patienten mit Grad-3- und -5-Nebenwirkungen wurden Zielvolumina nahe des Mediastinums bestrahlt, die nunmehr als ungeeignet für eine stereotaktische Bestrahlung angesehen werden. Im Fall der fatalen Blutung blieb allerdings unklar, ob diese Folge einer Tumorinfiltration oder einer Radionekrose der rechten Arteria pulmonalis war.

WHO Grade	Lung n = 27	Liver n = 24	Complication
0	19 (70%)	17 (71%)	
1/2	6 (22%)	7 (29%)	Nausea, vomiting, pain, fever, chills (few hours)
			Symptomatic pneumonitis (n = 1) and hepatitis (n = 1) (6 weeks)
3	1 (4%)	0	Chronic ulcerous esophagitis (4 months)
4	0	0	
5	1 (4%)	0	Fatal bleeding lung (9 months)

for liver targets (Figure 4). 81% (13/16) patients with pulmonary targets and 100% (9/9) with hepatic targets died because of systemic progression of disease. Actuarial overall survival of the patients with curative treated lung cancer was 60% after 1 year and 40% after 2 years. Three patients died of metastases (cerebrum, liver, lung), three patients are alive without disease, one patient is alive with brain metastases and one with a local recurrence. Median survival is 9.5 months (4–33 months). Actuarial overall survival for curative treated liver metastases was 100% after 12 and 24 months compared to 62% and 33% for palliative treated targets. Nevertheless the median follow-up in the curative treated group is only 4 months (2–26 months).

Treatment Related Toxicity

Stereotactic irradiation generally could be performed on an outpatient basis due to very low acute toxicity (Table 4). In 70% (19/27 targets in the lung and 17/24 targets in the liver) no side effects occurred. In 22% (6/27) of lung and 29% (7/24) of liver targets grade 1–2 toxicities according to the WHO score were observed, mostly related to only one fraction. Acute side effects were fever, chills or pain with a typical onset a few hours after irradiation. In liver targets additionally nausea and/or vomiting might occur at the same time as the other effects. These symptoms ceased spontaneously after a few hours and could be treated by analgesics and antipyretics (metamizole, paracetamol), antiemetics (metoclopramide, ondansetron) or anti-edematous therapy (prednisolon). One patient developed a symptomatic pneumonitis after 6 weeks with dry cough and subfebrile temperature and another showed signs of radiogenic hepatitis with loss of appetite and the feeling of weakness. Both patients were treated successfully with dexamethason over 6 weeks with no acute or persistent impairment of organ function. No acute grade 3–5 toxicity was observed. The lung tissue surrounding the targets showed slowly increasing fibrosis in the high-dose area without clinical effect. This fibrosis is a long-term process with continuous change of shape even over years, which apparently could be difficult to distinguish from a tumor recurrence. After 6 weeks targets in the liver showed a hypodense area outside the target corresponding to the volume with a fraction dose of 7–8 Gy, which decreased spontaneously within 3–6 months and was interpreted as radiogenic edema.

Relevant late toxicity occurred in two patients, both with targets in the lung close to the mediastinum: Irradiation of a metastasis of rectal cancer with 4 × 7 Gy adjacent to the lower

esophagus led to chronic ulcerous esophagitis after 4 months (WHO grade 3). The second target was a local recurrence of lung cancer, which was pre-irradiated with 63 Gy a year ago and increasingly compressed the right pulmonary artery. This patient was re-irradiated with 3 × 10 Gy and died 9 months later due to a fatal bleeding from the lung. This event was accounted as treatment related toxicity (WHO grade 5), although it remained unclear whether the bleeding of the vessel was due to tumor arrosion or radiogenic necrosis.

Discussion

Although extracranial stereotactic irradiation is an emerging treatment modality with an increasing number of institutions working in this field [2, 3, 6–8, 10–13, 18, 20], only very few institutions have published their clinical results. Clinical data from original papers on local control of pulmonary and hepatic targets have been published by Blomgren et al [2, 3], Uematsu et al [18], Nakagawa et al [13] and Herfarth et al [6, 8] (the second publication [2] of Blomgren et al included treatment results from the first [3] so that clinical results will only be discussed from the most recent paper [2]).

Most authors report crude local control rates instead of actuarial data due the small number of cases analyzed or the small number of local failures observed. Published crude local control rates range from 88–97% for targets in the lung and 78–100% for targets in the liver, which corresponds to the local control rates of 85% and 83% in the presented study. Herfarth et al [6] reported an actuarial local control rate for hepatic targets of 71% after 12 months and 67% after 18 months for all 55 of 60 evaluable targets, which as well corresponds to the results of the presented study of 76% and 61% after 12 months and 24 months. Potentially the actuarial local control rates for lung cancer and liver metastases treated with curative intention will be superior to those treated palliative. Nevertheless the number of these targets is still too low to draw conclusions.

Interestingly Herfarth et al [6] reported a learning curve due to dose escalation from 12 to 24 Gy/isocenter and for definition of adequate security margins for the PTV within the first six patients. Excluding these targets from Kaplan-Meier analysis led to an actuarial local control rate of 81% after 18 and 24 months. Such a learning curve was not observed in our study, maybe because dose prescription and security margins for PTV definition were based on the experience of Blomgren and Lax, so that no dose adjustment had to be performed according to clinical results.

Nevertheless direct comparison of published treatment results and interpretation of potential reasons for local failure is difficult because of the variety of treatment concepts used and parameters reported: the treatment concepts range from single dose irradiation [6], single dose +/- normofractionated radiotherapy [13], hypofractionated irradiation [2, 3, 20] to stereotactic irradiation in 5–15 fractions [18]. For comparison of the results of the published studies some data (follow-up as median or mean, tumor volume in cm^3 or tumor diameter in cm) was recalculated (e.g. the median of the CTV from Blomgren et al [2, 3] or the CTV from target diameter and overall survival in Uematsu et al [18]). A summary of treatment concepts, numbers of treated targets, follow-up and local control rates is shown in Tables 5a and 5b.

Comparison of the impact of dose and fractionation on local control between the different concepts is impossible due to the lack of clinical or experimental data on the biological effect of single doses of 10–24 Gy. Therefore only the clinical parameters such as follow-up and target volume (CTV and PTV) can be used for analyzing differences between the reported results. While the median follow-up period of about 6–9 months with a maximum of about 30–40 months is similar in most groups, the volume of the irradiated targets shows major differences: for pulmonary targets the CTV is 15 cm^3 (3–198 cm^3 [2, 3]), 0.5–55 cm^3 [18] (calculated by the formula diameter^3/2 from the published tumor diameter of 1–4.8 cm) and 40 cm^3 (5–126 cm^3) for chest-wall targets, respectively 4.5 cm^3 (0.8–13 cm^3) for intrapulmonary targets [13]. Compared to these volumes the CTVs of pulmonary targets in the presented study are significant larger with a median volume of 57 cm^3 (5–277 cm^3). Comparison of the volume of hepatic targets shows that the CTV in the presented study at least doubles the CTV of previously published data: median was 50 cm^3 (9–516 cm^3) compared to 22 cm^3 (3–622 cm^3) respectively 24 cm^3 (2–263 cm^3) [2, 3] and 10 cm^3 (1–132 cm^3) [8]. Nevertheless the role of volume for local control remains unclear due to the small number of reported cases and the inhomogeneity of treatment parameters. But the local control rates achieved in the presented study might indicate that even larger volumes as reported up to now can be treated successfully. The limiting factor for the irradiated volume is the functional volume of lung and liver receiving a fraction dose of less than 7 Gy in a hypofractionated approach of 3 × 10 Gy/65%-isodose. Within the 7-Gy isodose transient (edema) or definitive functional damage as necrosis, fibrosis or veno-occlusive disease [1] have to be considered. Nevertheless the precise pathologic process related to certain dose levels has not been evaluated yet.

Surgery still is the standard treatment for small non-small cell lung cancer of Stage cT1 and cT2 cN0 cM0 as it is for solitary metastases in the lung and liver of certain primaries as colorectal cancer. However, some patients are not amenable for surgery because of medical impairment or disadvantageous localization of the tumor as bilobar metastases in the lung or liver. In this situation the local control rates of extracranial stereotactic radiotherapy have to compete with other treatment modalities such as laser induced thermotherapy (LITT) [19], radiofrequence ablation (RFA) [15] or percutaneous ethanol instillation (PEI) [17], which are available for the treatment of hepatocellular carcinoma and liver metastases. While for radiofrequence ablation local control rates for liver metastases of 70% [15], for percutaneous ethanol instil-

lation up to 86% [17] are reported, for laser induced thermotherapy local control rates of up to 98% have been achieved by experienced authors [19]. Not only under the assumption that patient and target selection have some impact on the published results, the local control rates for extracranial stereotactic irradiation of 80–100% are at least similar to the local control rates reported of other modalities. Additionally the radiotherapeutic approach has some advantages compared to laser induced thermotherapy, percutaneous ethanol instillation or radiofrequence ablation: it is non-invasive, is not limited by blood coagulation or other medical parameters, is not painful for the patient and can be performed generally on an outpatient basis. Serious side effects have not been observed, if doses of more than 7 Gy per fraction to organs at risk are avoided. Nevertheless targets close to the mediastinum or adjacent to organs at risk as esophagus, stomach, duodenum or small bowel, should be chosen with caution. Acute complications as bleeding, infections or necrosis due to thermal or chemical effects [5] have not to be considered because radiotherapy is non-invasive.

Table 5a. Comparison of published treatment results of stereotactic irradiation for targets in the lung. Data with * have been recalculated from the data of the original publications for easier comparison of results.

Tabelle 5a. Vergleich der bisher veröffentlichten Behandlungsergebnisse der stereotaktischen Bestrahlung von Zielvolumina in der Lunge. Die mit * versehenen Daten wurden aus den Angaben in den jeweiligen Publikationen nachträglich berechnet, um die Ergebnisse besser vergleichen zu können.

Author	Indication	No of targets	Dose/fractionation/normalization	Volume of CTV (median) (cm^3)	Median f/u (min-max) (months)	Local control (crude)	Local control (actuarial)
Blomgren et al [2]	Prim. tumors/ metastases	n = 17	3 × 10 to 2 × 15 Gy/65%-isodose	3–198 (15)*	8 (mean) (3.5–25)	16/17 (94%)	Not reported
Uematsu et al [18]	Prim. tumors/ metastases	n = 66	5–15 fractions 30–76 Gy/80%-isodose	1–4.8 cm tumor diameter 0.5–55 cm^3*	11 (3–31)	64/66 (97%)	Not reported
Nakagawa et al [13]	Metastases	n = 22	1 × 15 to 1 × 24 Gy "peripheral dose" +/- conv. fract. RT	Chest wall 5–126 (40) Central lung 0.8–13 (4.5)	10 (2–82)	20/21 (95%)	Not reported
Wulf et al (presented study)	Prim. tumors/ metastases	n = 27	3 × 10 Gy/65%-isodose	5–277 (57)	8 (2–33)	23/27 (85%)	76% (12/24 months)

Table 5b. Comparison of published treatment results of stereotactic irradiation for targets in the liver. Data with * have been recalculated from the data of the original publication of Blomgren et al [2] for easier comparison of results. The median of the follow-up for the targets of Blomgren et al could not be re-calculated because the f/u data are not published in detail. HCC: hepatocellular carcinoma; CCC: cholangiocellular carcinoma.

Tabelle 5b. Vergleich der bisher veröffentlichten Behandlungsergebnisse der stereotaktischen Bestrahlung von Zielvolumina in der Leber. Die mit * versehenen Daten wurden aus den Angaben der Publikation von Blomgren et al. [2] nachträglich berechnet, um die Ergebnisse besser vergleichen zu können. HCC: hepatozelluläres Karzinom; CCC: cholangiozelluläres Karzinom.

Author	Indication	No of cases	Dose/fractionation/normalization	Volume of CTV (median) (cm^3)	Median f/u (min-max) (months)	Local control (crude)	Local control (actuarial)
Blomgren et al [2]	HCC, CCC	n = 20	3 × 10 to 2 × 15 Gy/65%-isodose	3–622 (22)*	12 (mean) (1.5–38)	20/20 (100%)	Not reported
Blomgren et al [2]	Metastases	n = 21	3 × 10 to 2 × 15 Gy/65%-isodose	2–263 (24)*	9.6 (mean) (1.5–28)	20/21 (95%)	Not reported
Herfarth et al [6]	Metastases	n = 60	1 × 14 to 1 × 24 Gy/isocenter	1–132 (10)	5.7 (1–26) (78%)	47/60	All targets: 71% (12 months) 67% (18 months) After dose escalation: 81% (18 months)
Wulf et al (presented study)	Metastases CCC	n = 23 n = 1	3 × 10 Gy/65%-isodose	9–516 (50)	9 (2–28)	19/23 (83%)	76% (12 months) 61% (24 months)

Actuarial overall survival of stereotactically irradiated patients ranges between 60% [2] and 72% [6] after 12 months and 21–43% (presented study) after 24 months. Median survival in our study was 8 months for patients with pulmonary targets and 9 months with hepatic targets. The majority of these patients (81% of pulmonary and 100% of hepatic targets) died from systemic progression of disease. Herfarth et al [6] reported systemic progression of 45% of patients with liver metastases for colorectal cancer and 78% from breast cancer. For lung targets median survival was 9.8 months (2–82 months) [13] and 12 months (6–31 months) for primary lung tumors, respectively 9 months (3–24 months) for lung metastases [18]. However, according of the published data half of the patients treated with stereotactic radiotherapy will decease within a time of 8–9 months. This life expectancy is low compared to surgical data, where for patients with resected liver metastases of colorectal cancer a median survival of 20–74 months is reported [4]. Nevertheless at clinical introduction of a new treatment approach patients with increased risk for treatment failure and progression of disease (tumor size and site, other tumor manifestations, medical condition) will accumulate, while the patients with more advantageous factors will be treated by the standard modality as surgery or chemotherapy.

It was the purpose of the presented study to introduce the stereotactic approach to extracranial targets and to evaluate local control rates and treatment toxicity. Therefore patient and target selection might be improved due to the clinical experience to achieve a maximum of patient benefit. The accumulating data, however, suggest high local control and a favorable therapeutic index of extracranial stereotactic radiotherapy in circumscribed pulmonary and hepatic lesions. To achieve more substantial information on the role of extracranial stereotactic radiotherapy on targets in the lung and liver in Germany protocols are in preparation, which prospectively will compare a stereotactic single dose irradiation to a hypofractionated approach. Theses studies will evaluate the efficiency of treatment and the role of dose, fractionation and volume for local control and side effects under prospectively defined conditions.

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