EUROPEAN JOURNAL OF CANCER 45 (2009) 2947–2959

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Review

Stereotactic body radiation therapy for liver metastases

Omar Dawood [a], *Anand Mahadevan* [b], *Karyn A. Goodman* [c,*]

[a] *Accuray Incorporated, Sunnyvale, CA, United States*
[b] *Department of Radiation Oncology, Beth Israel Deaconess Medical Center, Boston, MA, United States*
[c] *Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, United States*

ARTICLE INFO

Article history:
Received 27 May 2009
Accepted 19 August 2009
Available online 19 September 2009

Keywords:
Radiosurgery
Liver
Neoplasm metastasis
Colorectal neoplasms

ABSTRACT

Although resection is the standard of care for liver metastasis, 80–90% of patients are not resectable at diagnosis. Advances in combination chemotherapy, particularly with targeted agents, have increased tumour response and survival in patients with unresectable metastatic colorectal cancer, but these techniques have limitations and may be associated with high recurrence rates. Some autopsy series have shown that as many as 40% of patients with metastatic colorectal cancer have disease confined to the liver; aggressive local therapy may improve overall survival in such patients. Local control of liver metastases can also ease hepatic capsular pain to improve quality of life. Stereotactic body radiation therapy (SBRT) offers an alternative, non-invasive approach to the treatment of liver metastasis through precisely targeted delivery of radiation to the tumours while minimising normal tissue toxicity. Early applications of SBRT to liver metastases have been promising with the reports of 2-year local control rates of 71–86% and other studies reporting 18-month local control rates of 71–93%. While these data establish the safety of SBRT for liver metastases, more rigorous phase II clinical studies are needed to fully evaluate long-term efficacy and toxicity results. In the interim, this review stresses that SBRT of liver must be performed cautiously given the challenges of organ motion and the low toxicity tolerance of the surrounding hepatic parenchyma.

1. Introduction

The liver is a common site of metastases for a variety of primary malignancies including colorectal, lung, breast, bladder, oesophageal, head, neck and pancreas cancers, as well as cholangiocarcinomas and ocular melanomas.[1] Other more rare sources of liver metastasis include neuroendocrine tumours[2] and ovarian adenocarcinomas.[3] In the case of colorectal cancer, the liver is often the first site of metastatic progression. This is attributed to venous drainage from both the colon and rectum through the portal vein, which is a major source of blood supply to the liver. As a result, 15–25% of colorectal cancer patients will have liver metastases at the time of diagnosis and 50–70% of them will develop liver metastasis during the course of the disease.[4] In 2007, the incidence of colorectal cancer was estimated to be more than 150,000 new cases in the United States (US), with a slight predominance in men. These cases result in more than 52,000 annual deaths.[5]

When possible, surgical resection is the standard of care for liver metastasis (Table 1). Unfortunately, 80–90% of patients are not resectable at diagnosis.[6] The high rate of

* *Corresponding author:* Address: Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, United States. Tel.: +1 212 639 3983; fax: +1 212 639 2417.
E-mail address: goodmank@mskcc.org (K.A. Goodman).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.08.011

Table 1 – Summary of treatment approaches for liver metastasis.

Treatment	Overview	Contraindications	Complications	Survival
Surgical resection	Curative intent. Invasive surgical removal of diseased liver tissue. Only 10–20% of patients are resectable; 10–15% of patients with recurrent disease are candidates for re-resection[57]	Non-treatable primary tumour, >70% liver involvement, liver failure, surgically unfit, widespread metastatic disease, distant peritoneal disease, extensive nodal disease, pulmonary, bone or CNS metastases[7,8]	Surgical mortality 1–2%.[7,8] Complication rate at least 25% including myocardial infraction (1%), pneumonia (5–10%) pulmonary embolism (1%), liver failure (3–8%), intraoperative haemorrhage (2–5%), bile leak (4%) and perihepatic abscess (5–10%)[58]	For colorectal metastasis, 5-year survival generally reported as 25–40%,[4,7] but some studies have reported up to 60%[8,9] in which cases patient selection, imaging and technique probably play a role in higher rates.[9] 10–15% of patients have recurrent disease[6]
Radiofrequency ablation (RFA)	An alternating current delivers heat to the target cells inducing necrosis. Can be used on non-resectable lesions in conjunction with surgery[59,60]	Limited to non-resectable/ non-operable lesions.[6] Lesion must be smaller than 3 cm[4]	Minor complications 2.4–12%, major complications 0–5.8%.[13] Complications include fever, malaise, arthralgias, hypotension, hepatic abscess, liver abscesses, portal vein thrombosis, pleural effusion, colon perforation and renal insufficiency.[2,61] Up to 40% of lesions recur, 12% of which are at the treatment site within 1 year[15]	For colorectal metastasis, RFA alone has 3-year survival rates of 28–46%, and a 5-year survival rate of 25%.[13] When complete resection is not possible RFA can provide modest benefit over chemotherapy[62]
Chemotherapy	Palliative when used as sole treatment			Flurouracil 3-year survival is 5–10%[63]
Chemotherapy + resection	Chemotherapy can allow up to 12.5% of unresectable patients to become resectable[12]	Unresectable but medically operable patients	Complications (17–19%) include postoperative liver failure; biliary leaks; reoperations for hepatic bleeding, parietal haemorrhage or bowel perforation; fluid collections; pleural effusions, pulmonary infections and cardiac arrhytmias[12]	For colorectal metastases, 5-year overall survival 33%, disease-free survival 30%; high (66–88%) recurrence after resection[12]
Resection + chemotherapy	Adjuvant intravenous systemic chemotherapy after resection	Typical contraindications include cardiac dysfunction, renal dysfunction, extrahepatic metastases, local relapse of primary tumour, incomplete resection of liver metastases, chemotherapy within a year of resection, radiotherapy within a month before resection or resection more than 35 days before chemotherapy[10]	Complications include Grade 3 or 4 haematologic, stomatitis, nausea, diarrhea or neuropathy observed in 24.7% of patients; with 12% having more than one toxicity[10]	For colorectal metastases, 5-year disease-free survival of 43% compared to 35% without chemotherapy. Overall survival is 50%[10]
Cryoablation	Freeze-thaw cycle using liquid nitrogen induces destruction of cells but may not destroy all cells	Unresectable	Complications include biliary fisulae, coagulopathy, myoglobinuria, hepatic abscesses and pleural effusions. Mortality rate 1.5% due to either cryoshock or liver failure[4]	For colorectal metastases, the 5-year survival rate is 13%, and the 3-year survival rate is 32%. When used after resection 3-year rates become similar to resection[4]

Radiation therapy (RT)	3D-CRT for partial irradiation of the liver	Unresectable and untreatable by other methods. Liver must be otherwise healthy to reduce risk of RILD	RILD is primary concern. Doses must be limited to 30–35 Gy for the whole liver, but can be increased with partial irradiation	For colorectal metastases, 17–20 month survival[4]
SBRT	Non-invasive approach to treatment of liver metastasis through precisely targeted delivery of the radiation dose to the malignancies while minimising normal tissue toxicity	Unresectable and untreatable by other methods		See individual results in Table 3. No long-term follow-up available

unresectable liver metastasis stems both from an advanced stage at diagnosis and, recently, from the use of extensive staging, typically including MRI and FDG-PET imaging, to ensure disease is resectable and rule out occult metastatic disease prior to surgery.[6] This staging not only prevents unnecessary resections, but also allows unresectable patients earlier access to alternative therapies. As a result of the improved patient selection, resection rates have improved from the historically reported 5-year survival rates of 25–40%[4,7] to the more recently reported 5-year survival rates of up to 60%.[8,9] Similarly, surgical-resection-related mortality rates are now reported as low as 1%.[4,7] Unfortunately, the use of adjuvant systemic therapy has not contributed to survival after resection.[10]

For unresectable patients, advances in combination chemotherapy, particularly with targeted agents, have resulted in response rates of up to 50% and a doubling of median survival from 10 to 20 months in patients with metastatic colorectal cancer.[11] Chemotherapy has also been used to downstage lesions, making 12.5% of patients eligible for surgery.[12] Although other techniques have been used for tumour downstaging, the majority of patients with liver metastases remain ineligible for surgery. A number of local, less invasive treatment approaches including radiofrequency ablation (RFA), transarterial chemoembolisation and cryoablation have shown promising local control results,[4,13,14] but each of these techniques has limitations and variable high recurrence rates[15] (Table 1).

Some autopsy series have shown as many as 40% of the patients with metastatic colorectal cancer have disease confined to the liver.[16] Patients with untreated liver metastases have a 5-year survival rate of less than 3%.[17] These observations suggest that in some subsets of patients with limited disease in the liver ('oligometastases'), aggressive local therapy may improve overall survival. Furthermore, local control of liver metastases is useful for palliation of hepatic capsular pain to improve the quality of life for the remainder of these patients' lives.

Radiation therapy is an established palliative modality, but the optimal role for radiation therapy in the treatment of liver tumours has not been well defined. Historically, the liver was thought to be a relatively radiosensitive organ, and it was difficult to achieve the radiation doses necessary to eradicate gross tumours without causing radiation-induced liver disease (RILD) which occurs approximately 4–8 weeks following radiation therapy.[18] RILD symptoms include ascites, increased weight, increased girth and increased levels of alkaline phosphatase. To limit RILD, studies have shown that whole liver irradiation must remain under 30–35 Gy with the conventional 2 Gy per fraction.[19–21] These studies have also shown that, in addition to the total dose the liver receives, the volume of irradiated liver is crucial. Emami et al. have shown that when only two-thirds of the liver is irradiated doses up to 35 Gy are permissible and when only one-third of the liver is irradiated permissible doses increase to 50 Gy.[22] These results have been substantiated in several dose escalation studies.[23] For selected patients, aggressive focal radiation can deliver tumouricidal doses using three-dimensional (3D) techniques, including intensity modulated radiotherapy (IMRT). Experience with 3D treatment planning has

allowed the safe irradiation of two-thirds of the normal liver to 48–52.8 Gy and one-third of the liver to 66–72.6 Gy with a fraction size 1.5–1.65 Gy.[24–27] Unfortunately, further dose escalation with conventional radiation therapy techniques risks injury to adjacent abdominal structures, such as the bowel, stomach, biliary system and vascular structures.

Stereotactic body radiation therapy (SBRT) offers an alternative, non-invasive approach to the treatment of liver metastasis. The goal of SBRT is to deliver a high dose to the target, thereby providing better local tumour control, while limiting dose to surrounding healthy tissue, thereby potentially decreasing complication rates. Early applications of SBRT to liver metastases have been promising (Table 3). While these data establish the safety of stereotactic radiation therapy for liver metastases, all SBRT treatments must be performed cautiously given the challenges of organ motion and the low radiation tolerance of the surrounding hepatic parenchyma. In this review, we summarise the treatment considerations for liver metastases using SBRT.

2. Overview of SBRT

SBRT may be seen as an extracranial extension of stereotactic radiosurgery (SRS), the accurate delivery of multiple beams of cross-fired radiation to ablate an intracranial target. Leksell[28] developed the frame-based radiosurgery technology called the Gamma Knife (Elekta AB, Stockholm, Sweden) which today is widely accepted for the treatment of intracranial diseases, including primary and metastatic lesions. In early reports, Blomgren et al. described the extension of a frame-based, SRS-like treatment approach to the liver and lung.[29,30] Shortly thereafter, Hamilton et al. used a similar frame-based approach to treat the spine.[31] These were the initial reports of what would come to be called SBRT.

Table 2 – Summary of commercial stereotactic body radiation therapy devices for the treatment of liver metastases.

Device	Radiation Source	Treatment Delivery	Tumour Motion
CyberKnife® Radiosurgery System (Accuray Incorporated, Sunnyvale, CA)	X-band linear accelerator. 6 MV photon energy with variable aperture collimator	Linac mounted to 6D robotic arm. To minimise dose gradient, delivers hundreds of non-coplanar beams per fraction. Isocentric and non-isocentric beam delivery	Image guidance throughout treatment corrects for intrafraction rotational and translational target movements. Targeting corrections managed via robotic repositioning. Patient breathes freely during treatment delivery without gating or breath-holding techniques
Novalis TX (Varian Medical Systems and BrainLab)	6–20 MV photon energy. Multileaf collimator with 120 2.5-mm leaves	Varian C-Series platform. Linac mounted to gantry c-arm with clockwise/counter-clockwise rotations. Delivers radiation through circular cone arcs or fixed-shape conformal beams (typically 7) via the micromultileaf collimator. Isocentric beam delivery	Integrates BrainLAB's imaging system to detect intrafraction target movement. Detected movements require treatment interruption and manual patient realignment via 6D couch. During treatment delivery, respiratory gating and a body frame are used to limit movement
Varian Trilogy™ (Varian Medical Systems, Inc., Palo Alto, CA)	6 MV photon energy. Multileaf collimator with 120 5-mm leaves	Varian C-Series platform. (See Novalis TX details noted above)	Pre-treatment image guidance for patient alignment via cone beam CT or portal imaging. Optical imaging system monitors movement of patient's surface during treatment delivery. If patient movement is detected during treatment then the system halts treatment while patient repositioning occurs by physical movement of the patient treatment couch before resuming the treatment process
Novalis® (BrainLAB, Inc, Germany)	6 MV photon energy. Micromultileaf collimator with 26 leaf pairs	Varian 6EX platform. Linac mounted to gantry c-arm with clockwise/counter-clockwise rotations. Fixed-shape conformal beams deliver radiation via micromultileaf collimator. Isocentric beam delivery	Same as Novalis TX, see above
TomoTherapy Hi-Art® System (TomoTherapy Incorporated, Madison, WI)	6 MV photo energy. Multileaf collimator with 64 binary leaves	Gantry-ring geometry delivers radiation helically around the patient. Isocentric beam delivery	Megavoltage CT scanner and 3D laser positioning system used for pre-treatment patient positioning. Patient immobilisation, breath-holding and gating are used to reduce movement during treatment

2.1. *Targeting tumours that move with respiration*

SBRT requires precise localisation of the target tissue. In the liver, and other extracranial sites, tumour motion must be accounted for to ensure proper delivery of the radiation to the tumour and to avoid unnecessary dose to the surrounding healthy tissue. Although it is possible to determine the range of motion in pre-treatment imaging and to construct an internal target volume (ITV) that includes that range, many clinicians agree that such a method necessitates the irradiation of too much healthy tissue.[32] Several technical solutions to this problem have been developed; Table 2 summarises these, and highlights the primary components needed for SBRT of liver tumours.

Current methods of dealing with tumour motion may be called motion-restrictive or motion-compensating. In one method of motion restriction, the patient is immobilised in a stereotactic frame and his/her breathing is restricted by an abdominal compression device.[33] In another motion restriction method, the patient is taught to hold his/her breath during pre-treatment imaging and during treatment, typically for 20–35 s; radiation is delivered to the location that was shown in pre-treatment imaging to include the tumour. Error in motion-restrictive methods is introduced because motion is never entirely eliminated with abdominal compression,[33] or because patients may not precisely reproduce the levels of inspiration with breath-holding approaches. The relation between the level of inspiration and internal tumour location may also vary in breath-holding approaches, introducing another source of error. These errors may be mitigated, in part, by careful coaching and monitoring of the patient's breathing, and through image-guided setup and verification.[34] However, because of the potential errors additional margins around the tumour are used to assure adequate radiation coverage. Breath-holding can also be a difficult task for lung cancer patients.

Motion-compensating systems include respiratory gating and tumour tracking. In respiratory gating, the radiation beam is turned off and on during specific times in the respiratory cycle when the tumour (which is often marked with implanted fiducials) has been shown in pre-treatment imaging to be in a specific location. Some studies have shown that this method allows a reduction in treatment margins relative to the conditions without motion compensation.[35,36] Interfraction changes in breathing patterns and intrafraction changes in the correlation between external and internal markers may introduce additional, and sometimes extensive, errors. Indeed, Korreman et al. concluded that margins could only be reduced by gating if these changes were taken into account by appropriate image guidance between and within sessions.[37] In addition, respiratory gating requires users to set the percentage of session time during which the beam is turned on, i.e. the 'gating window'. Setting a larger 'gating window' results in a higher percentage of the respiratory cycle in which the beam is on and allows the treatment to be delivered more quickly; however it requires that a larger field be radiated. The goal is to set the percentage low, which limits the volume of irradiated tissue and also lengthens the treatment session. In practice, gating windows of 25–40% are common.

The motion tracking approach to motion compensation uses a treatment system that follows the movement of the tumour and adjusts for any changes in tumour motion in real-time, throughout treatment, while the patient breathes normally without restriction. Motion tracking is driven by the correlation between the location of fiducial markers near the tumour, as detected in orthogonal X-rays, and the location of external markers on the patient's chest. The correlation model is built just after patient setup and is updated throughout a treatment fraction each time X-rays are obtained (about once every 30–90 s). The ability of motion tracking to reduce tumour motion-related error has been documented.[38,39] The choice of treatment device and the mechanism for handling tumour motion impacts both the underlying treatment and patient selection. The impact of how tumour motion is handled during treatment will be discussed as applicable in the remainder of this review, but a detailed discussion and analysis of the various treatment devices is outside the scope of this review and has been presented elsewhere.[40]

3. SBRT considerations

SBRT of liver metastases begins with patient selection, followed by pre-treatment imaging, treatment planning, possible fiducial placement, treatment delivery and follow-up. SBRT are highly specialised for individual patients, and will differ depending on the treatment device used and how tumour motion is handled. In the following, we highlight the general considerations necessary for SBRT of liver metastases and point out the issues relating to treatment devices and tumour motion compensation approaches when possible. While these considerations are presented sequentially, inevitably each consideration impacts others and in practice all must be considered simultaneously. It is also important to understand that SBRT is a multi-disciplinary process and involvement of a complete clinical team from initial patient consultation through treatment and follow-up is critical to the process.

3.1. *Patient selection*

Patients generally considered eligible for SBRT of liver metastases are unresectable with adequate hepatic function. The presence of progression or untreated primary disease and widespread metastatic disease are also usual exclusionary criteria. The number and size of lesions, and consequently the volume and function of uninvolved liver treated, is of special concern for the liver due to the risk of RILD. A variety of criteria have been applied to date, including restrictions based on the number of tumours (typically 3 or less), the size of the tumours (typically less than 6 cm), the proximity to adjacent organs and either the volume or percent of normal liver that receives a specific dose (typically greater than 700–1000 cm^3 of normal liver must receive less than 15 Gy in 3 fractions). While these inclusionary criteria vary among the published studies, the overall message is clear: constraints must be applied to ensure that a sufficient volume of healthy liver tissue is not irradiated to a high dose. For patients with

Table 3 – Published stereotactic body radiation therapy liver metastases studies.

Publication	Histology (*N* patients, *M* tumours)	Total dose (Gy) fractions isodose line (%)	Outcomes	Complications	Follow-up	Notes
Radiosurgery for tumours in the body: clinical experience using a new method (Blomgren et al., 1998)[50]	*N* = 17 *M* = 21, also primary tumours	20–45 Gy (mean 34.1 Gy) 2–4 fractions 65%	Tumour growth arrested in 10, tumour size reduced in 4, disappeared in 4 and 1 local failure. Crude local control rate 95%	Two cases of haemorrhagic gastritis Minor: Nausea, fever, chills	Mean 9.6 months (range 1.5–24)	5 mm transversal and 10 mm longitudinal CTV margins
Feasibility of frameless stereotactic high-dose radiation therapy for primary or metastatic liver cancer (Sato et al., 1998)[49]	*N* = 4 *M* = 5, also primary tumours	50–60 Gy Median 10 fractions (range 5–10) 80%	100% crude local control	5% Grade 1–2; 5% Grade 3–4 toxicities	Median 10 months (range 3–25)	
Stereotactic single-dose radiation therapy of liver tumours: results of phase I/II trial (Herfarth et al., 2001)[54]	*N* = 37 *M* = 56, also primary tumours	14–26 Gy 1 fraction 80%	Actuarial local tumour control 75%, 71% and 67% at 6, 12 and 18 months Higher doses improved local control 12 local failures during follow-up	No serious complications noted Intermittent loss of appetite or mild nausea, moderate singultus, fever	Median 5.7 months (range 1–26.1)	6 mm transversal and 10 mm longitudinal PTV margin Tumour size less than 6 cm Additional cytotoxic chemotherapy was performed synchronously or during follow-up in 12 patients
Stereotactic radiotherapy of targets in the lung and liver (Wulf et al., 2001)[41]	*N* = 20 *M* = 23, also other primary tumours	30 Gy 3 fractions 65%	Actuarial local control 76% and 61% for 1 and 2 years	29% Grade 1–2 toxicities. Fever, chills or pain, nausea and vomiting. One patient had symptomatic pneumonitis and another patient had radiogenic hepatitis. No Grade 3–5 toxicities	Median 9 months (range 2–28)	2–3 mm GTV margin; 5 mm transversal and 10 mm longitudinal PTV margin
Assessment of focal liver reaction by multiphasic CT after stereotactic single-dose radiotherapy of liver tumours (Herfarth et al., 2003)[55]	*M* = 32, other primary tumours	Median 22 Gy 1 fraction 80%	All but 1 patient had a tumour response to SBRT 9 of 36 patients (25%) recurred during follow-up	No major side-effects and no patient developed clinical signs of RILD Focal liver reaction visible radiobiologically; sharply demarcated areas 2–4 months after SBRT The radiation reaction might be falsely diagnosed as recurrent tumours	18 months	

Univariate analysis of factors correlated with tumour control probability of three-dimensional conformal hypofractionated high-dose radiotherapy for small pulmonary or hepatic tumours (Wada et al., 2004)[53]	$M = 5$, other primary and metastatic tumours	45 Gy 3 fractions 90–100%	71% 2-year tumour control for liver (includes HCC) 95% tumour control for lesions <3 cm, 58% for lesions >3 cm (liver and lung primary and mets)	No serious toxicity reported	Median 19.3 months (range, 4–52 months)	5 mm transversal and 10 mm longitudinal PTV margins
A phase I trial of stereotactic body radiation therapy (SBRT) for liver metastases (Schefter et al., 2005)[52]	$N = 18$	36–60 Gy	All doses were well tolerated. Results of this study formed the basis for an ongoing Phase II SBRT study of 60 Gy over three fractions for liver metastases	No patients experienced dose-limiting toxicity. One patient died most likely as a result of progressive liver metastases, 4 patients died of complications from progressive extra hepatic metastases and 1 patient died from preexisting medical comorbities unrelated to SBRT	Median 7.1 months (range, 3.8–12.3 months)	The authors recommend that $\geqslant 700\ cm^3$ of normal liver receives $\leqslant 15$ Gy
	$M = 24$	3 fractions 80–90%	No local control/survival indicated			No GTV margins 5 mm transversal and 10 mm longitudinal PTV margins
Individualised image-guided iso-NTCP based liver cancer SBRT (Dawson et al., 2006)[44]	$N = 34$, with other primaries	1.5–25.2 Gy (median 16.8)	No dose-limited toxicity observed	Accrual continues		CTV is 8 mm margin of GTV. PTV margin around GTV for dose and a PTV margin around CTV for microscopic disease. Min PTV margin 5 mm but highly individualised
Phase II study on stereotactic body radiotherapy of colorectal metastases (Hoyer et al., 2006)[51]	$N = 44$, other met sites	45 Gy 3 fractions 95%	Data not broken down for liver metastases alone	Data not broken down for liver mets alone		5 mm transversal and 10 mm longitudinal PTV margins
Interim analysis of a prospective phase I/II trial of SBRT for liver metastases (Kavanagh et al., 2006)[48]	$N = 36$	60 Gy	Actuarial local tumour control 93% at 18 months	One patient with metastatic colon cancer with 3 treated lesions had intra-hepatic progression outside treated regions. Then treated with selective internal radiation therapy and developed Grade 3 gastritis	19 months	The authors recommend that $\geqslant 700\ cm^3$ of normal liver receives $\leqslant 15$ Gy

(*continued on next page*)

Table 3 – (*continued*)

Publication	Histology (*N* patients, *M* tumours)	Total dose (Gy) fractions isodose line (%)	Outcomes	Complications	Follow-up	Notes
Interim analysis of a prospective phase I/II trial of SBRT for liver metastases (Kavanagh et al., 2006)[48]	N = 36	60 Gy	Actuarial local tumour control 93% at 18 months	One patient with metastatic colon cancer with 3 treated lesions had intra-hepatic progression outside treated regions. Then treated with selective internal radiation therapy and developed Grade 3 gastritis	19 months	The authors recommend that $\geqslant 700\ cm^3$ of normal liver receives $\leqslant 15$ Gy
		3 fractions	1233 cm^3 of uninvolved liver got less than 15 Gy	1 Grade 3 skin toxicity (oedema, breakdown) attributed to hot spot 1 cm below skin		5 mm transversal and 10 mm longitudinal PTV margins
		80–90%	Survival not reported	No Grade 4+ toxicity		
Image-guided respiratory gated hypofractionated stereotactic body radiation therapy (H-SBRT) for liver and lung tumours: Initial experience (Wurm et al., 2006)[36]	N = 3 M = 4	79.2 Gy 11 fractions	100% local control	No toxicity	Not specified	CTV = GTV. PTV = CTV + 5 mm margin in all directions Focus of paper is motion
Stereotactic body radiation therapy for primary and metastatic liver tumours: A single institution phase I–II study (Mendez Romero et al., 2006)[46]	N = 17	37.5 Gy (3 patients received 30 Gy because of microscopic disease, small bowel proximity or volume of normal liver)	1- and 2-year local control: 100% and 86% for metastases patients	Two non-classic cases of RILD	Median 12.9 months (range .5–31)	Initially, 5–10 mm margin to PTV, but now use fiducials and margins are individualised
	M = 34, plus	3 fractions	Actuarial survival at 1 and 2 years: 85% and 62% for metastases	Two metastases patients had elevated gamma glutamyl transferase (Grade 3) and one had asthenia (Grade 3)		Complications possibly due to percent healthy tumour volume receiving >15 Gy
	Plus HCCs	65%		One Grade 2 ascites Late toxicity was observed in one metastases patient who developed a portal hypertension syndrome with melena (Grade 3)		

Hypofractionated stereotactic body radiation therapy (SBRT) for limited hepatic metastases (Katz et al., 2007)[47]	N = 69 M = 174	30–55 Gy 7–20 fractions 80%	The median survival was 14.5 months Progression-free survival was 46% and 24% at 6 and 12 months No patients developed Grade 3 or higher toxicity	The most common side-effects were fatigue and nausea 28% experienced increase in liver function tests (Grades 1–2)	Median 14.5 months	7 mm transversal and 10 mm longitudinal margins The dose per fraction and total dose were determined using the dose volume histogram of organs at risk, with a preferred schedule of 50 Gy in 5 Gy fractions over 2 weeks
Dose escalation study of stereotactic body radiotherapy for liver malignancies (Goodman et al, 2009)[56]	N = 26 M = 19, also 7 primary tumours	18–30 Gy 1 fraction 80%	The median survival for all patients was 28.6 months. The 1-year and 2-year overall survival rates for those treated for metastases were 61.8% and 49.4%, respectively	Acute Grade 1 toxicity was observed in 9 patients, acute Grade 2 toxicity in 1 patient and late Grade 2 gastrointestinal toxicity in 2 patients	Median 17.3 months (range 2–55)	No CTV margin. 3–5 mm PTV margin. In absence of 4D-CT, a greater than 5 mm margin added

multiple lesions or large lesions this becomes a significant patient selection issue.

3.2. *Patient setup*

During SBRT patients are positioned on the treatment couch in supine position. In order to obtain precise delivery of radiation to the target tissue, the patient's position must be reproduced during all pre-treatment diagnostics and all treatment sessions. Patients treated with liver SBRT require a diagnostic multiphasic contrast-enhanced helical CT scan to allow localisation of the target tumour; MRI and FDG-PET imaging are also frequently performed to obtain accurate registration of the tumour with identifiable areas of enhancement and hypermetabolic activity, respectively, to best identify the extent of microscopic disease extension. In addition, 4D-CT scans can be acquired to obtain details on tumour motion during respiration. When real-time tumour motion tracking is employed, internal fiducial markers (or seeds) must be implanted into the liver tumour to allow monitoring of the tumour movement during treatment. These fiducials are typically implanted percutaneously through CT-guidance or ultrasound guidance. For ideal translational and rotational motion tracking, 3–5 fiducial markers must be placed in good, non-coplanar geometry with respect to each other. To allow for any potential fiducial seed movement, treatment is generally performed a week or so after implantation.

3.3. *Target definition*

Once pre-treatment imaging has been performed the gross tumour volume (GTV) is outlined on the CT images. Next, a clinical target volume (CTV) can be defined to allow for the inclusion of margins based on microscopic extension. Typical CTV margins for microscopic extension are 2–3 mm,[41] although in many published cases no specific CTV margin is applied. Last, the planning target volume (PTV) is defined by applying margins to account for any inaccuracies in the delivery system. The size of the PTV margin expansion depends on the type of motion handling employed. Typically much smaller margins, on the order of 1.5 mm, are required for devices that track respiratory motion, as opposed to devices that employ motion compensation or the use of stereotactic frames, which require larger margins on the order of 5–10 mm.[42]

3.4. *Treatment dosimetry and fractionation*

The liver is a parallel functioning organ that appears capable of receiving high doses of radiation as long as a sufficient volume of healthy liver tissue is spared. A variety of tissue sparing dosimetry approaches have been applied for liver metastases SBRT. These approaches typically involve ensuring that a specific volume, or percentage of healthy tissue, receives less than a specified dose. The fractionation of the treatment dose will also determine the dose that the normal liver can tolerate. The earliest of these approaches stems from a joint University of Colorado and Indiana University study which recommended at least 700 cm^3 of healthy liver tissue receive less than 15 Gy over 3 fractions. Another popular approach is to limit the V15 and V21 (volume of normal

liver tissue receiving 15 Gy and 21 Gy, respectively) to less than 50% and 30%, respectively, in 3 fractions.[43] Single-fraction schemes use V7 and V12 for similar 'normal' (uninvolved liver volumes). These models obviously assume that there is adequate volume (>700 cc) of normal uninvolved liver. A tolerance-based dose prescription using the Normal Tissue Complication Probability (NTCP) model is another approach.[44,45] These two approaches are based on liver tolerance and allow flexible dose prescription to the tumour. To date, a variety of fractionation schedules have been applied ranging from single fraction to hypofractionation regiments as outlined in Table 3 with the majority of the published results applying a total of 30–60 Gy in 3 fractions.

3.5. *Potential complications*

While SBRT of liver metastases has the potential of producing RILD, very few clinical reports of RILD following SBRT exist. Minor complications, especially prevalent in early SBRT applications, include nausea, loss of appetite, vomiting, fever and chills. Grade 2 complications such as ascites[46] and increased liver function tests,[47] along with Grade 3 complications including gastritis,[48] elevated gamma glutamyl transerase,[46,49] asthenia[46] and skin toxicity[48] have occurred occasionally. Mendez Romero et al.[46] also reported two cases of non-classic RILD but no higher grade toxicities have been reported. The absence of high-grade complications, however, should be viewed as a consequence of careful treatment planning and cautious dose schedules rather than as a sign to treat more aggressively.

Neighbouring critical structures, especially those of nearby normal tissues such as the stomach and duodenum, are also potential sites for complications. In the early work of Blomgren et al., one patient experienced haemorrhagic gastritis following irradiation of less than one-third of the stomach to more than 7 Gy during each of two treatment sessions, and another patient experienced a duodenal ulcer after part of the distal stomach and proximal duodenum received 5 Gy in each of 4 treatment sessions.[50] Hoyer et al. also observed complications of a colonic ulceration and duodenal ulceration when part of the intestine received greater than 30 Gy.[51] These experiences demonstrate the need for careful treatment planning and delivery to limit irradiation of these highly sensitive neighbouring normal tissues. While exact dose constraints are not available, in cases where the lesion location prohibits limiting the stomach and intestine to receiving less than 10 Gy, Schefter et al urges extreme caution.[52] In addition, point doses to the duodenum should not exceed > 10 Gy per fraction for 3 fractions,[48,52] when a significant part of the duodenum circumference is involved a more conservative dose limit such as 8 Gy per fraction for 3 is preferable.

4. Clinical Applications and Results of SBRT for Liver Metastases

Several SBRT clinical applications for liver metastases have been reported (Table 3). These studies include a variety of fractionation schedules and dosing schemes that can be categorised as single-fraction, multi-fraction and limited hypofractionation. To date, the majority of these clinical applications have targeted multiple-fraction treatment approaches using 2 or more fractions.

Blomgren et al. delivered 20–45 Gy (mean 34.1 Gy) in 2–4 fractions to a combination of 17 primary tumours and 21 liver metastases in the first published SBRT liver treatment.[50] Crude local control with a 9.6-month mean follow-up was 95% and two cases of haemorrhagic gastritis were observed. Wulf et al. delivered a total dose of 30 Gy in 3, 10-Gy fractions (30 Gy in 3 fractions) to 23 liver metastases in a report that also included primary tumours and some lung targets.[41] Actuarial local control of liver metastases was 76% at 1 year and 61% at 2 years with no Grade 3 or higher toxicities. Wada et al. delivered 45 Gy in 3 fractions to 5 liver metastases (treatment of primary liver and lung lesions was also reported in this study).[53] Local control of liver lesions was approximately 85% at 6 months and 71% at 18 months. Local control was enhanced for smaller lesions, with 95% local control at 18 months for lesions less than 3 cm in diameter (liver and lung lesions combined) versus 58% for lesions over 3 cm. No serious adverse events were reported. Mendez Romero et al. utilised 12.5 Gy in 3 fractions or 5 Gy in 5 fractions for patients with primary and secondary liver lesions.[46] One- and two-year local control rates were 94% and 82% for all patients and 100% and 86% for patients with metastases. Survival ranged from 92% overall at 6 months to 70% overall at 18 months. They noted three instances of acute Grade 3 or higher toxicity, including a patient with Childs B cirrhosis that died secondary to liver decompensation, oesophageal bleeding and infection, 2 weeks post-radiosurgery. More recently, Hoyer et al. reported a phase II study in which patients with colorectal hepatic metastases were treated with 15 Gy in 3 fractions. They demonstrated a two-year local control rate of 86% and a 38% overall two-year survival rate.[51] This treatment was well tolerated. In another phase I study for liver metastases, Kavanagh et al. dose escalated to 20 Gy in 3 fractions without reaching maximum tolerated dose (MTD). These investigators limited 700 cc of normal liver to less than 15 Gy and included tumours up to 6 cm in maximum dimension.[48,52]

Herfarth and colleagues conducted a phase I/II trial of single-fraction SBRT for liver metastases.[54,55] The dose was escalated from 14 to 26 Gy, with the 80% isodose surrounding the planning target volume. Median tumour size was 10 cm^3 (range 1–132 cm^3). All patients tolerated the treatment well without any major side-effects. Eleven patients experienced intermittent loss of appetite or mild nausea for 1–3 weeks after treatment. None of the treated patients developed clinically detectable RILD (weight gain, ascites and newly developed increase of alkaline phosphatase concentration). The overall actuarial local tumour control rates were 75%, 71% and 67% at 6 months, 12 months and 18 months of follow-up, respectively. There was a statistically significant difference in Kaplan–Meier estimates of local tumour control between tumours treated with 14–20 Gy versus 22–26 Gy, but the local control may have also been influenced by a 'learning' phase. The investigators noted that local control was improved in patients treated later in the study after establishing the proper margin expansion; in these patients the actuarial

local tumour control rate was 81% at 18 months. Stratification by size did not reveal a statistically significant difference in the local control rate for larger lesions (>15 cm^3) compared with smaller ones (<15 cm^3) in the 22–26 Gy range.

Most recently, Goodman et al. performed a single fraction phase I dose escalation study for primary and metastatic liver tumours.[56] The prescribed radiation dose was escalated from 18 to 30 Gy at 4 Gy increments. All patients tolerated the treatment well without developing a dose-limiting toxicity. Acute Grade 1 toxicity was observed in 9 patients, acute Grade 2 toxicity in 1 patient and late Grade 2 gastrointestinal toxicity in 2 patients. For the liver metastasis patients, the 1-year and 2-year overall survival rates were 61.8% and 49.4%, respectively. The investigators conclude that single-fraction SBRT for liver lesions demonstrates promising local tumour control with minimal acute and long-term toxicity.

In addition to the single-fraction and multiple-fraction treatment approaches, three clinical studies have applied limited hypofractionation using more than 5 fractions. In the earliest of these, by Sato et al., a total of 50–60 Gy was delivered in 5–10 fractions (median 10 fractions) on 5 liver metastases and 4 primary tumours. The crude local control rate was 100% for a median 10 months follow-up with an observed rate of 5% for Grades 1–2 and 5% for Grades 3–4 toxicities. Wurm et al. delivered a total dose of 74.8–79.2 Gy in 8–11 fractions to 3 patients with 4 metastases. They observed 100% local control with no toxicity at an unspecified follow-up.[36] More recently, Katz et al. delivered 30–55 Gy in 7–20 fractions to 174 liver metastases and 69 primary tumours. For liver metastases, the median survival was 14.5 months, and progression-free survival was 46% and 24% at 6 and 12 months. No patients developed Grade 3 or higher toxicity.

5. Future outlook

The published results on SBRT of liver metastases are encouraging. Yet, the range of different doses and fractionation schedules used demonstrates the current lack of a consensus regarding the optimal SBRT for liver metastases. It is important to note that there is tremendous variation in the devices available for SBRT and close attention must be paid to how one is addressing issues of hepatic tumour motion. Techniques that track tumour motion and therefore allow clinicians to limit the treatment volume to only that which is clinically relevant may be ideal in ensuring the delivered dose reaches the tumour and that the surrounding normal tissue is maximally spared. While the results to date are promising and have demonstrated significant potential for SBRT for liver metastases, more rigorous phase II clinical studies are needed to fully evaluate long-term efficacy and toxicity results.

Conflict of interest statement

Dr. Dawood is Vice President of Clinical Development for Accuray Incorporated. Dr. Mahadevan has received speaking honoraria from Accuray Incorporated. Dr. Goodman has no conflicts to report.

REFERENCES

1. Grover A, Alexander Jr HR. The past decade of experience with isolated hepatic perfusion. *Oncologist* 2004;**9**(6):653–64.
2. Mazzaglia PJ, Berber E, Siperstein AE. Radiofrequency thermal ablation of metastatic neuroendocrine tumors in the liver. *Curr Treat Options Oncol* 2007;**8**(4):322–30.
3. Bojalian MO, Machado GR, Swensen R, Reeves ME. Radiofrequency ablation of liver metastasis from ovarian adenocarcinoma: case report and literature review. *Gynecol Oncol* 2004;**93**(2):557–60.
4. Kemeny N. Management of liver metastases from colorectal cancer. *Oncology (Williston Park)* 2006;**20**(10):1161–76. 1179; discussion 1179–80, 1185–6..
5. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. *CA Cancer J Clin* 2007;**57**(1):43–66.
6. Small R, Lubezky N, Ben-Haim M. Current controversies in the surgical management of colorectal cancer metastases to the liver. *Isr Med Assoc J* 2007;**9**(10):742–7.
7. Poston GJ, Adam R, Alberts S, et al. OncoSurge: a strategy for improving resectability with curative intent in metastatic colorectal cancer. *J Clin Oncol* 2005;**23**(28):7125–34.
8. Lochan R, White SA, Manas DM. Liver resection for colorectal liver metastasis. *Surg Oncol* 2007;**16**(1):33–45.
9. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg* 2002;**235**(6):759–66.
10. Portier G, Elias D, Bouche O, et al. Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial. *J Clin Oncol* 2006;**24**(31):4976–82.
11. Kelly H, Goldberg RM. Systemic therapy for metastatic colorectal cancer: current options, current evidence. *J Clin Oncol* 2005;**23**(20):4553–60.
12. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg* 2004;**240**(4):644–57. discussion 657–8..
13. Garrean S, Hering J, Saied A, Helton WS, Espat NJ. Radiofrequency ablation of primary and metastatic liver tumors: a critical review of the literature. *Am J Surg* 2008;**195**(4):508–20.
14. Vogl TJ, Zangos S, Eichler K, Yakoub D, Nabil M. Colorectal liver metastases: regional chemotherapy via transarterial chemoembolization (TACE) and hepatic chemoperfusion: an update. *Eur Radiol* 2007;**17**(4):1025–34.
15. Solbiati L, Livraghi T, Goldberg SN, et al. Percutaneous radiofrequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. *Radiology* 2001;**221**(1):159–66.
16. Weiss L, Grundmann E, Torhorst J, Hartveit F, Moberg I, Eder M, et al. Haematogenous metastatic patterns in colonic carcinoma: an analysis of 1541 necropsies. *J Pathol* 1986;**150**(3):195–203.
17. Wagner JS, Adson MA, Van Heerden JA, Adson MH, Ilstrup DM. The natural history of hepatic metastases from colorectal cancer. A comparison with resective treatment. *Ann Surg* 1984;**199**(5):502–8.
18. Lawrence TS, Robertson JM, Anscher MS, et al. Hepatic toxicity resulting from cancer treatment. *Int J Radiat Oncol Biol Phys* 1995;**31**(5):1237–48.
19. Austin-Seymour MM, Chen GT, Castro JR, et al. Dose volume histogram analysis of liver radiation tolerance. *Int J Radiat Oncol Biol Phys* 1986;**12**(1):31–5.
20. Russell AH, Clyde C, Wasserman TH, Turner SS, Rotman M. Accelerated hyperfractionated hepatic irradiation in the

management of patients with liver metastases: results of the RTOG dose escalating protocol. *Int J Radiat Oncol Biol Phys* 1993;**27**(1):117–23.
21. Lyman JT. Complication probability as assessed from dose-volume histograms. *Radiat Res Suppl* 1985;**8**:S13–9.
22. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991;**21**(1):109–22.
23. Dawson LA, Ten Haken RK, Lawrence TS. Partial irradiation of the liver. *Semin Radiat Oncol* 2001;**11**(3):240–6.
24. Borgelt BB, Gelber R, Brady LW, Griffin T, Hendrickson FR. The palliation of hepatic metastases: results of the Radiation Therapy Oncology Group pilot study. *Int J Radiat Oncol Biol Phys* 1981;**7**(5):587–91.
25. Lawrence TS, Ten Haken RK, Kessler ML, et al. The use of 3-D dose volume analysis to predict radiation hepatitis. *Int J Radiat Oncol Biol Phys* 1992;**23**(4):781–8.
26. Leibel SA, Pajak TF, Massullo V, et al. A comparison of misonidazole sensitized radiation therapy to radiation therapy alone for the palliation of hepatic metastases: results of a Radiation Therapy Oncology Group randomized prospective trial. *Int J Radiat Oncol Biol Phys* 1987;**13**(7):1057–64.
27. Jackson A, Ten Haken RK, Robertson JM, et al. Analysis of clinical complication data for radiation hepatitis using a parallel architecture model. *Int J Radiat Oncol Biol Phys* 1995;**31**(4):883–91.
28. Leksell L. Stereotactic radiosurgery in trigeminal neuralgia. *Acta Chir Scand* 1971;**137**:311–4.
29. Lax I, Blomgren H, Naslund I, Svanstrom R. Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. *Acta Oncol* 1994;**33**(6):677–83.
30. Blomgren H, Lax I, Naslund I, Svanstrom R. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. *Acta Oncol* 1995;**34**(6):861–70.
31. Hamilton AJ, Lulu BA, Fosmire H, Stea B, Cassady JR. Preliminary clinical experience with linear accelerator-based spinal stereotactic radiosurgery. *Neurosurgery* 1995;**36**(2):311–9.
32. Murray B, Forster K, Timmerman R. Frame-based immobilization and targeting for stereotactic body radiation therapy. *Med Dosim* 2007;**32**(2):86–91.
33. Heinzerling JH, Anderson JF, Papiez L, et al. Four-dimensional computed tomography scan analysis of tumor and organ motion at varying levels of abdominal compression during stereotactic treatment of lung and liver. *Int J Radiat Oncol Biol Phys* 2008;**70**(5):1571–8.
34. Eccles C, Brock KK, Bissonnette JP, Hawkins M, Dawson LA. Reproducibility of liver position using active breathing coordinator for liver cancer radiotherapy. *Int J Radiat Oncol Biol Phys* 2006;**64**(3):751–9.
35. Guckenberger M, Krieger T, Richter A, et al. Potential of image-guidance, gating and real-time tracking to improve accuracy in pulmonary stereotactic body radiotherapy. *Radiother Oncol* 2008.
36. Wurm RE, Gum F, Erbel S, et al. Image guided respiratory gated hypofractionated stereotactic body radiation therapy (H-SBRT) for liver and lung tumors: initial experience. *Acta Oncol* 2006;**45**(7):881–9.
37. Korreman SS, Juhler-Nottrup T, Boyer AL. Respiratory gated beam delivery cannot facilitate margin reduction, unless combined with respiratory correlated image guidance. *Radiother Oncol* 2008;**86**(1):61–8.
38. Nioutsikou E, Seppenwoolde Y, Symonds-Tayler JR, et al. Dosimetric investigation of lung tumor motion compensation with a robotic respiratory tracking system: an experimental study. *Med Phys* 2008;**35**(4):1232–40.
39. Seppenwoolde Y, Berbeco RI, et al. Accuracy of tumor motion compensation algorithm from a robotic respiratory tracking system: a simulation study. *Med Phys* 2007;**34**(7):2774–84.
40. Andrews DW, Bednarz G, Evans JJ, Downes B. A review of 3 current radiosurgery systems. *Surg Neurol* 2006;**66**(6):559–64.
41. Wulf J, Hadinger U, Oppitz U, et al. Stereotactic radiotherapy of targets in the lung and liver. *Strahlenther Onkol* 2001;**177**(12):645–55.
42. Goodman KA. Stereotactic radiosurgery for liver malignancies using the CyberKnife. In: Urschel Jr HC, editor. *Treating tumors that move with respiration*. Heidelburg: Springer; 2007. p. 217–25.
43. Dawson LA, Ten Haken RK. Partial volume tolerance of the liver to radiation. *Semin Radiat Oncol* 2005;**15**(4):279–83.
44. Dawson LA, Eccles C, Craig T. Individualized image guided iso-NTCP based liver cancer SBRT. *Acta Oncol* 2006;**45**(7):856–64.
45. Tse RV, Hawkins M, Lockwood G, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol* 2008;**26**(4):657–64.
46. Mendez Romero A, Wunderink W, Hussain SM, et al. Stereotactic body radiation therapy for primary and metastatic liver tumors: a single institution phase i–ii study. *Acta Oncol* 2006;**45**(7):831–7.
47. Katz AW, Carey-Sampson M, Muhs AG, et al. Hypofractionated stereotactic body radiation therapy (SBRT) for limited hepatic metastases. *Int J Radiat Oncol Biol Phys* 2007;**67**(3):793–8.
48. Kavanagh BD, Schefter TE, Cardenes HR, et al. Interim analysis of a prospective phase I/II trial of SBRT for liver metastases. *Acta Oncol* 2006;**45**(7):848–55.
49. Sato M, Uematsu M, Yamamoto F, et al. Feasibility of frameless stereotactic high-dose radiation therapy for primary or metastatic liver cancer. *J Radiosurg* 1998;**1**(3):233–8.
50. Blomgren H, Lax I, Goranson H, et al. Radiosurgery for tumors in the body: clinical experience using a new method. *J. Radiosurg* 1998;**1**(1):63–74.
51. Hoyer M, Roed H, Traberg Hansen A, et al. Phase II study on stereotactic body radiotherapy of colorectal metastases. *Acta Oncol* 2006;**45**(7):823–30.
52. Schefter TE, Kavanagh BD, Timmerman RD, et al. A phase I trial of stereotactic body radiation therapy (SBRT) for liver metastases. *Int J Radiat Oncol Biol Phys* 2005;**62**(5):1371–8.
53. Wada H, Takai Y, Nemoto K, Yamada S. Univariate analysis of factors correlated with tumor control probability of three-dimensional conformal hypofractionated high-dose radiotherapy for small pulmonary or hepatic tumors. *Int J Radiat Oncol Biol Phys* 2004;**58**(4):1114–20.
54. Herfarth KK, Debus J, Lohr F, et al. Stereotactic single-dose radiation therapy of liver tumors: results of a phase I/II trial. *J Clin Oncol* 2001;**19**(1):164–70.
55. Herfarth KK, Hof H, Bahner ML, et al. Assessment of focal liver reaction by multiphasic CT after stereotactic single-dose radiotherapy of liver tumors. *Int J Radiat Oncol Biol Phys* 2003;**57**(2):444–51.
56. Goodman KA, Anderson EM, Maturen KE, et al. Dose escallation study of stereotactic body radiotherapy for liver malignancies. *Int J Radiat Oncol Biol Phys*, in press.
57. Khatri VP, Petrelli NJ, Belghiti J. Extending the frontiers of surgical therapy for hepatic colorectal metastases: is there a limit? *J Clin Oncol* 2005;**23**(33):8490–9.
58. Fong Y, Blumgart LH, Cohen AM. Surgical treatment of colorectal metastases to the liver. *CA Cancer J Clin* 1995;**45**(1):50–62.
59. Elias D, Goharin A, El Otmany A, et al. Usefulness of intraoperative radiofrequency thermoablation of liver

tumours associated or not with hepatectomy. *Eur J Surg Oncol* 2000;**26**(8):763–9.
60. Pawlik TM, Izzo F, Cohen DS, Morris JS, Curley SA. Combined resection and radiofrequency ablation for advanced hepatic malignancies: results in 172 patients. *Ann Surg Oncol* 2003;**10**(9):1059–69.
61. de Baere T, Risse O, Kuoch V, et al. Adverse events during radiofrequency treatment of 582 hepatic tumors. *AJR Am J Roentgenol* 2003;**181**(3):695–700.
62. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg* 2004;**239**(6):818–25. discussion 825–7.
63. Thirion P, Michiels S, Pignon JP, et al. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: an updated meta-analysis. *J Clin Oncol* 2004;**22**(18):3766–75.