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Dose to organ at risk and dose prescription in liver SBRT

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ABSTRACT

Stereotactic body radiation therapy (SBRT) is delivered in a curative intent to many primary and secondary tumors.

Concerning liver metastasis, SBRT can be safely delivered using one to five fractions. An excellent local control is obtained with doses from 20 to 60 Gy. For primary hepatic tumors, results are also good, but the risk of hepatic toxicity related to liver pre-existent pathology must be taken into account. Radiation induced liver disease (RILD) is not frequent in its classical presentation, but modifications of liver enzymes are often observed. Other toxicities of SBRT on the duodenum, small bowel and biliary tract are also described. With respect to contraindications and dose limitations on surrounding structures, SBRT is well tolerated and takes place among curative treatment of liver tumors, as surgery, radiofrequency and embolization.

1. Background

Stereotactic body radiation therapy (SBRT) is defined as an ablative irradiation modality, the most often delivered in less than 5 fractions, taking into account positioning uncertainties and breathing motions with image-guided radiation therapy (IGRT). Liver SBRT aims to treat hepatic metastasis in a curative intent as surgery and radiofrequency. Primary liver tumors also benefit from SBRT either exclusively or as a bridge to transplantation.[1,2]

To obtain a favorable therapeutic index, irradiation schedule and targeting have to be strictly evaluated. Efficient doses on tumor must be defined, as well as tolerable doses on healthy liver and other critical structures.

2. Dose prescription and treatment issues

SBRT provides high doses per fraction, delivered daily or every second day. The number of fractions vary from one[3–6] to six, with most authors treating liver with 3–5 fractions. Table 1

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Table 1 – Prescription, local control and toxicity from selected series.

	Sample	Dose	Prescription	Local control	Toxicity > = grade 3
Blomgren et al. (1995)	14 pts with mets	7 Gy–45 Gy	ICRU point	50% response rate	1 hemorragic gastritis
Herfarth et al. (2004)	37 pts with mets	1x(14–26 Gy)	Isocenter 80%isodose surrounding PTV	71% 1 year 68% 2 years	None
Schefter et al. (2005) Rusthoven et al. (2005)	63 mets	3 × 12 Gy To 3 × 20 Gy	Isodose surrounding PTV (80%–90%)	92% at 2 years 100% for tumors < 3 cm	DLT not reached
Wulf et al. (2006)	39 pts with mets 5 with HCC	3 × 10 Gy 3 × 12.5 Gy 1 × 26 Gy	65% isodose	100% HCC last follow up 66% 2 years mets	None
Mendez-Romero et al. (2006)	34 pts with mets 11 with HCC	3 × 12.5 Gy At risk patients 5 × 5 Gy	65% isodose line	84% 2 years	1 classic RILD (liver failure and fatal infection, pt Child B initial) 1 portal hypertension with melena 2 elevation GGT Grade3
Hoyer et al. (2006)	44 pts with mets	3 × 15 Gy	Isocenter	79% 24 mths	One lethal hepatic failure 1 colic perforation (surgery) 2
McCammon et al. (2009)	81 pts Mets and primaries	3 × 10 Gy to 3 × 20 Gy	Isodose surrounding PTV (80%–90%)	100% (54–60 Gy) 89% (31.1–53.9 Gy)	None
Lee et al. (2009)	68 pts with mets	Median 41.8 Gy 6 fns 2 wks	Envelop isodose Max in PTV 140%	71% 1 year	Grade 5 SBO + grade 4 bleed (progression) SBO abdominal hernia Grade 3 gastritis/oesophagitis 2
Rusthoven et al. (2009)	47 pts with 63 mets	3 × 12–20 Gy	80 or 90% isodose	92% 2 years	1 grade 3 soft tissue toxicity
Goodman et al. (2010)	26 pts 40 lesions 19 mets 5 IHC and CHC	18 Gy to 30 Gy single dose Cyber Knife	Isodose surrounding PTV	77% 1 year	No limiting toxicity
Sintzing et al. (2010)	14 pts 19mets (CCR)	24 Gy single dose Cyberknife	Isodose surrounding PTV	87% 1 year	No toxicity
Tse et al. (2008)	47HCC IHC	6 × 9-–0 Gy	Unspecified	65% 1 year	10 Grade 3 liver enzymes 1 bleeding from tumor duodenal connection (lethal) 1 SBO (lethal) CTP progression A-B 7/41
Andolino et al. (2011)	60 HCC	3 × 14 (CTP)A 5 × 8 (CTP B)	80% isodose	90% 2 years	20% progression CTP class None nonhematologic tox. > = 3 Within 3 months
Scorsetti et al. (2012)	61 pts with mets 71 lesions	3 × 25 Gy	Mean dose (VMAT)	94% 12 mths	1 grade 3 chest wall pain
Bujold et al. (2013)	10 HCC	6 × 4 Gy To 6 × 9 Gy		87% 1 year	
Huerta et al. (2015)	77 pts 97 HCC	3 × 15 Gy Cyberknife		99% 1 year	
Meyer et al. (2015)	14 pts 17 mets	35–40 Gy single dose		Local control 2.5 years 100%	No limiting toxicity
Andratschke et al. (2015)	74 pts 91 mets	5–12.5 Gy 3–5 fns	60–95% surrounding isodose	Local control 74.7% 1 year	

Mets: metastasis
Pts: patients
HCC: hepatocellular carcinoma
IHC: intra hepatic cholangiocarcinoma
CTP class: Child Turcotte Pugh class
SBO: small bowel obstruction
Fx: fractions
VMAT: volumetric modulated arc therapy
Fns: fractions

synthesizes the data from different studies in terms of radiotherapy planning, local control, and toxicity.

The first reported studies used doses extrapolated from conventional radiotherapy.[7–9] Then, prospective trials were conducted taking into account radiobiological parameters and following dose escalation protocols.[10,11]

Dose to the target is most often defined on the prescription isodose surrounding the PTV, which varies from 65 to 90%, and sometime on the isocenter.[7,12] Using intensity modulated radiation therapy (IMRT), the dose is prescribed to the mean dose in the PTV, and is less heterogeneous.[6]

From a radiobiological point of view, the question of whether a classic radiobiological modeling, with the linear-quadratic (LQ) model, is appropriate for large doses per fraction remains debated. For Kirkpatrick,[13] the underlying mechanisms implied by the LQ model do not reflect the vascular and stromal damages produced at the high doses per fraction encountered in radiosurgery, and ignore the impact of radioresistant subpopulations of cells. It has been hypothesized that SBRT may cause significant vascular damage in tumors, leading to indirect cell death.[14] Anyway, a recent review[15] concluded that "the available preclinical and clinical data do not support a need to change the LQ". The possibility of additional biological effects resulting from endothelial cell damage or enhanced tumor immunity is also discussed, as is the increased importance of tumor hypoxia in tumor response to SBRT.[16]

Main factors to impact the local control are the dose delivered, the target volume and the tumor type.

2.1. *Dose*

The dose delivered is the most important factor affecting local control. Prospective trials with dose escalation demonstrate this dose effect relation.[10,17–22,43]

Andratschke[10] treated 71 patients with 91 metastasis (mets). Treatment consisted of 3–5 fractions with 5–12.5 Gy/fraction prescribed to the surrounding 60–95% isodose. Median local recurrence-free interval was 23 months with a local control rate of 74.7%, 48.3% and 48.3% after 1, 2 and 3 years, respectively. Only minimum biologically effective dose (BED) to gross tumor volume (GTV) remained as an independent significant factor for local control in multivariate analysis. No local recurrences were observed in lesions ($n = 12$) which received a minimal BED to the GTV of 120 Gy (alpha/beta = 10).

McCammon et al.[18] reported the data of 141 consecutive patients with 246 pulmonary or hepatic lesions (65 primaries, 181 metastasis) treated with three-fraction SBRT from Oct. 1999 through Aug. 2005. On univariate analysis, increased dose (either nominal or Equivalent Uniform Dose (EUD) and smaller Gross Tumor Volume were significant predictors of higher local control). Lesions treated to a nominal dose of 54 Gy or greater had a 3-year actuarial local control rate of 89.3% compared with 59.0% and 8.1% for those treated to 36–53.9 Gy and less than 36 Gy. On multivariate analysis, only increased nominal dose and EUD retained statistical significance.

Information resumed in Table 1 show that primitive or secondary hepatic tumors can be treated with SBRT as an ablative treatment with a local control higher than 75% at the end of the first year after treatment. The dose required for a favorable result of the radiotherapy treatment might be 24–30 Gy in a single dose, 45–60 Gy in 3 fractions, 40–50 Gy in 5 fractions, 48–60 Gy in 6 fractions.[1,10,18,23,24]

2.2. *Volume of the tumor (Gross Tumor Volume GTV)*

In most articles, a tumor volume appears as an independent factor predictive of the local control of a tumor treated with SBRT.[3,18,25,26] Lee et al.[25] describes the outcome of SBRT for hepatic metastasis from different origins, the local control is related to tumor volume with a 75 ml threshold.

On the other hand, Rusthoven et al.[26] analyzing the outcome of 63 secondary lesions treated with SBRT in 47 patients shows that the 2-year LC was 100% for mets smaller than 3 cm compared with 77% (95% CI, 43%–92.2%) for lesions greater than 3 cm.

2.3. *Effectiveness compared between primary and mets*

Most of the studies concern metastasis only or primary tumors only but some series included a mix of metastasis and primaries. By performing analysis on primary tumors (HCC, IHC) and mets, these studies allow to analyze the outcomes and toxicities of these 2 populations treated with the same protocol.[4,18,20,27] The differences observed between metastasis and HCC in term of toxicity of treatments and survival is related to hepatic comorbidities (cirrhosis) rather than tumor radiosensitivity. Local control at one year is similar between the two populations. For example, Wulf observed a 100% local control of HCC at 15 months vs. 92% for metastasis.

This is confirmed by the results observed in specific CHC studies[9,28] with local controls around 80% at one year. Cholangiocarcinoma is a bad prognosis primary liver tumor presenting a low sensitivity to conventional radiotherapy even when associated with chemotherapy. It is interesting to note that in Tse's article,[28] the 10 patients presenting a cholangiocarcinoma responded to the SBRT as well as HC. In the same way, Barney et al.[11] present a population of 10 cholangiocarcinomas irradiated on primary site, the recurrence or a metastasis at a dose between 45 and 60 Gy in 3–5 fractions with a 100% local control but with distant recurrence in the liver in four patients.

2.4. *Other prognostic factors*

Hoyer et al.[12] describes other prognostic factors related to improved local control including smaller tumor volumes, potentially non-CRC metastases, metachronous liver metastases and absence of previous chemotherapy.

Table 2 – Dose-volume constraints for organs at risk with Biologic Equivalent Dose (BED) from selected studies.

Organs at risk	Study	Dose – volume constraint (VGy)	Biologic Equivalent Dose
Liver (alpha/beta 3)	Herfarth (2001) Wulf (2006) Mendez Romero (2006)	V12 < 30% V7 < 30% D30 < 7 Gy/D50 < 5 Gy V21 < 33% V15 < 50%	V60 < 30% V29.3 < 50% 3 fx V12.4 < 30%/V7.8 < 50%
Duodenum (alpha/beta 8)	Wulf (2006) Mendez Romero (2006) Tse (2008)	D100 < 7 Gy D5 cc < 21 Gy V30 < 0.5 cc	1 fx 13.1 Gy max/3 fx 9 Gy max 3 fx V39 < 5 cc/5 fx V32 < 5 cc V 48.8 < 0.5 cc
Bowel (alpha/beta 8)	Herfarth Wulf Mendez Romero Tse	12 Gy max D100 < 7 Gy D5 cc < 21 Gy V30 < 0.5 cc	30 Gy max 1 fx 13.1 Gy max/3 fx 9 Gy max 3 fx V39.4 < 5 cc/5 fx V32 < 5 cc V 48.8 < 0.5 cc
Stomach (alpha/beta 5)	Herfarth Wulf Mendez Romero Tse (2008)	12 Gy max D100 < 7 Gy D5 cc < 21 Gy V30 < 0.5 cc	40.8 Gy max 1 fx1 6.8 Gy max/3 fx10.3 Gy max 3 fx V50.5 < 5 cc/5 fx V38.6 < 5 cc
Spinal cord (alpha/beta 3)	Schefter (2005) Hoyer (2006) Mendez Romero (2006) Tse (2008)	18 Gy max 18 Gy max 15 Gy max V27 < 0.5 cc	54 Gy max 54 Gy max 3 fx 40 Gy max 5 fx30 Gy max V67.5 < 0.5 cc

3. Doses to organs at risk and toxicity (Table 2)

3.1. *Liver*

3.1.1. *Hepatic toxicity*

The main organ at risk for irradiation of hepatic tumors is the liver itself.[29,30] Radiation-induced liver disease (RILD) is the main radiotherapy toxicity.[29,31–33] Hepatic lesions have the character of veno-occlusive diseases (VOD). For classical RILD, symptoms occur 4 weeks after hepatic irradiation, with an increased weight, a fatigue, a non-icteric ascitis and a predominant increase of PALK. In general, the radiologic presentation on CT scan is a hypodensity which disappears a few months later.[3,20] In contrast, patients with a pre-existent hepatopathy, as cirrhosis or viral hepatitis, may present a transaminases increase and a jaundice within three months following hepatic irradiation corresponding to a non-classical post-radiation-hepatopathy.

3.1.1.1. Hepatic functions and tumor type.. Classical data show that the whole healthy liver can receive 30 Gy per fractions of 2 Gy[34] and has the feature of a parallel structured organ from a radiobiological point of view.[29,31] The comparison of studies should take into account the treatment duration and the doses per fraction according to the quadratic linear model.[31,35–37] The alpha/beta ratio for healthy liver is quite low, from 1.5[13] to 3[38]. Murphy et al.[33] postulates that the risk of hepatic toxicity for hypofractionated irradiation is overestimated in clinical practice when biological normalization is omitted. While analyzing 203 patients treated with conformational RT and intra-hepatic chemotherapy, Dawson et al.[39] showed in 2002 that the radiation-induced liver disease (RILD) threshold dose is 30 Gy, the 5% risk of RILD corresponding to a 32 Gy dose (2 Gy/fraction) for patients carrying metastasis and 28 Gy for primary hepatic tumors.[40] Andolino et al.[41] described a population of 60 patients treated from 2006 to 2009 for HCC associated with an A (36 patients) or B (24 patients) Child–Turcotte Pugh (CTP) score cirrhosis. Four patients out of the 8 patients with a CTP B score higher than 8, developed a hepatic failure during or immediately following the treatment. In this center, the indications of liver SBRT for this population are actually restricted to being a bridge for transplantation. For the other patients, it is proposed to limit the SBRT indications to patients with an A or B CTP score lower than or equal to 7 with a maximum tumor diameter lower than 6 cm and one to three lesions to be treated.

Taking these data into account, Pan et al.[31] proposed constraints for prescription on the liver minus GTV volume for non-uniform irradiation on healthy and pathological liver. For 3 fractions treatment: less than 15 Gy for metastasis, less than 13 Gy for HCC and less than 6 Gy for HCC with a CPT equal to or lower than B. In terms of critical volume, 700 ml of healthy liver should receive less than 15 Gy.

3.1.2. *Biliary tract toxicity*

Few papers are dedicated to biliary complications of SBRT. Eriguchi et al.[42] studied 50 patients irradiated on the central

biliary tract in 5 fractions for hepatic tumors at a total dose of 50 Gy for metastasis, 40 Gy for Child A HCC and 35 Gy for Child B HCC. The delineation of biliary tract was standardized and the dose volume histograms (DVH) of the biliary ducts were normalized for the length of the biliary duct irradiated. In this study, 2 grade I biliary stenosis occurred, one patient having received more than 20 Gy on 7 mm of the biliary duct presented a asymptomatic stenosis while the other one was treated twice and received more than 80 Gy on 13 mm of the left hepatic duct. The 7 patients who received more than 20 Gy on the gallbladder did not present any toxicity. In another article, Osmundson et al.[37] presented a population of 96 patients irradiated for primary or metastatic hepatic lesions treated between 2006 and 2013. The central biliary system was defined by the authors as a 15 mm expansion of the portal veina from the splenic convergence to the portal bifurcation. Fifty-one patients presented biliary or hepatic tumors and 45 metastasis. The median fraction number was 5 and 51% of patients received three fractions. Sixty-seven percent of patients had a Child A score, 28.1% a B score. Hepatobiliary grade 2 toxicities were observed for 23 patients (24%) and grade 3 toxicities for 18 patients (18.8%). The most frequent grade 3 toxicities were stenosis or biliary obstruction, the frequency being 20 fold higher for patients with cholangiocarcinoma (CCA). Two deaths related to biliary obstruction were observed, one of them for a patient with cholangiocarcinoma. The predictive factors in a univariate analysis were the cholangiocarcinoma and HCC histology, the presence of a stent during treatment and dosimetric factors. In a multivariate analysis, V_{BED10} 72 > 21 cc, V_{BED66} > 24 cc and a mean equivalent dose > 14 Gy on the central biliary hepatic tract were correlated with a toxicity risk > 3, as well as CCA histology and the presence of the stent. The authors propose 3 fractions treatment with the following constraints on the central biliary tract: V_{BED10} 72 < 21 cc and a V_{BED66} < 24 cc.[37]

3.1.3. *Stomach, duodenal and bowel toxicities*

The toxicity on the digestive tube is the one most frequently observed with hepatic SBRT. In general, these side effects are limited to a limited and transient bleeding, but some severe hemorrhages have been observed as well as perforations. Some data on duodenal SBRT toxicities have been identified with pancreatic tumor SBRT studies. In terms of radiobiology, the signification of doses is different for stomach (alpha/beta 5) and for bowel (alpha/beta 8).[1] For stomach, the proposed constraints in various studies range from 7 to 30 Gy maximum dose with a BED of 10.3–90 Gy_5.[1,3,4,17,28] Mendez Romero et al. constrained 5 cc of stomach to less than 21 Gy.[20] A few gastric acute toxicities have been reported. Kopek[43] describes an acute gastric toxicity with two grade 3 nausea for 44 patients. Herfarth et al.[3] also describes nausea and anorexia for 11 patients on the 37 accrued. Wulf et al.[4] proposes a prophylactic IPP or anti-H2 treatment during treatment of hepatic metastasis closed to the stomach.

Hoyer et al.[44] in a population of 22 patients receiving 45 Gy in 3 fractions delivered in 5–10 days for non operable pancreatic tumor whose size was higher than 6 cm, evaluated toxicity for the duodenum. Seventy-nine percent of the patients presented an acute toxicity, four patients (18%) developed a severe mucositis or a duodenal or gastric ulceration and one of them developed a perforation. In this study, the median volume receiving more than 30 Gy was 136 ml. In another work, the same team[12] analyzed a population of 64 patients with 141 hepatic metastasis from colorectal carcinoma. They received 3 fractions of 15 Gy delivered in 8 days. Two patients who received more than 30 Gy on the duodenum presented ulcerations with a favorable issue with medical treatment. One grade 3 toxicity among 15 diarrheas was reported in this study.[23]

For pancreatic tumor stereotaxy, Murphy et al.[33] have proposed a dosimetric model of duodenal toxicity. The duodenal delineation was specified with precision for 73 patients irradiated with a single 25 Gy dose 14 days after the last Gemcitabine treatment administration. Twelve patients presented grade 2–4 duodenal toxicities with a median interval of 6.3 months. The predictive dosimetric parameters were a V15 < 9.1 cc, a V20 < 3.3 cc and a Dmax > 23 Gy. Applying the same prescription to 27 cholangiocarcinoma, Kopek et al.[43] observed 22% of gastric or duodenal ulcerations after a median delay of 6.7 months requiring hospitalization and blood transfusion, a duodenal stenosis for 4 patients (11%), two of them requiring dilatation. The probability of grade higher or equal to 2 ulceration was correlated to the maximal dose delivered to 1 cc of the duodenum. The constraint followed by this group is one cc of the duodenum to get no more than 21 Gy in 3 fractions (V21Gy < 1 cc).

Bae et al.[45] evaluated the abdominal or pelvic SBRT toxicities delivering 33–60 Gy in three fractions for 202 patients. The grade 3 toxicity on the digestive tract was highly correlated to the V_{25} and to the overall time treatment. The severe bowel toxicity decreases from 50% to 4% when the V_{25} value is respectively higher or lower than 20 ml. In the same way, the grade 3 toxicity raised from 0 to 18% for an overall treatment time decreased from 8 to 4 days.

For small bowel, multiple proposals of limiting constraints have been defined in different studies: 12 Gy maximum,[3] 30 Gy maximum,[17,22] D100 < 7 Gy,[4] D5 < 21 Gy,[46] V30 < 0.5 cc.[47] However, no major toxicity has been reported.

3.1.3.1. Chest wall. As observed using lung SBRT, chest wall pains and sometimes rib fracture are observed after liver SBRT. They are of course more frequent after treating tumors close to the chest wall, and for doses above 50 Gy. Andolino et al.[38] proposes a Dmax less than 50 Gy and that less than 5 cc of the chest wall receive 40 Gy, if these objectives are compatible with adequate tumor coverage.

3.1.4. *Less exposed organs at risk*

Dose limitation proposals have also been formulated for less exposed organs at risk, and observing these constraints, no clinical toxicity have been documented.

Esophagus

A death due to bleeding on oesophageal varices, probably linked to cirrhosis without any other oesophageal toxicity, has been observed.[46]

Some liver SBRT protocols define constraints for esophagus. Méndez Romero et al.[46] limits to 5 cc the oesophageal volume receiving more than 21 Gy in 3–5 fractions.

A maximal dose of 14 Gy is proposed by Herfarth et al.,[3] and for Tse et al.[28] the V30 must be less than 0.5 cc.

Heart

Wulf et al.[4] proposed to limit the dose delivered to the hearth to 7 Gy and Tse et al.[28] proposed a $V_{40} < 0.5$ cc. No cardiac toxicity has been described.

Kydney

Constraints proposed for the two kidneys are V_{15} lower than 35%, and for the right kidney lower than 33%.[17,22,46]

Spinal cord

The dose has to be restricted to 18 Gy[12,17,22] or the V_{27} must be inferior to 0.5 cc.[28]

4. Conclusion

Considering the volume of data accumulated for the last twenty years concerning liver SBRT, this treatment appears no more as promising or experimental. The articles analyzed here show that it takes its place as a routine treatment among strategies of destruction of oligo metastases, as radiofrequency and surgery, in a curative intent. For treating primary hepatic tumors, SBRT is also an efficient alternative to local surgery, or chemo-embolization. Using strict criteria to protect healthy organs, SBRT associated with IGRT offers a high therapeutic index at least comparable to other ablative treatments. As a noninvasive approach it offers the opportunity of delivering iterative treatments in association with drug treatments, if necessary, leading to consider hepatic primary or secondary tumors as a chronic disease with the preservation of a good quality of life.

Conflict of interest

None declared.

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None declared.

REFERENCES

1. Sawrie SM, Fiveash JB, Caudell JJ. Stereotactic body radiation therapy for liver metastases and primary hepatocellular carcinoma: normal tissue tolerances and toxicity. *Cancer Control* 2010;**17**(2):111–9.
2. Tao C, Yang L-X. Improved radiotherapy for primary and secondary liver cancer: stereotactic body radiation therapy. *Anticancer Res* 2012;**32**(2):649–55.
3. Herfarth KK, Debus J, Wannenmacher M. Stereotactic radiation therapy of liver metastases: update of the initial phase-I/II trial. *Front. Radiat. Ther. Oncol* 2004;**38**:100–5.
4. Wulf J, Guckenberger M, Haedinger U, et al. Stereotactic radiotherapy of primary liver cancer and hepatic metastases. *Acta Oncol* 2006;**45**(7):838–47, http://dx.doi.org/10.1080/02841860600904821.
5. Stintzing S, Hoffmann RT, Heinemann V, Kufeld M. Muacevic a. Frameless single-session robotic radiosurgery of liver metastases in colorectal cancer patients. *Eur. J. Cancer* 2010;**46**(6):1026–32, http://dx.doi.org/10.1016/j.ejca.2010.01.008.
6. Scorsetti M, Arcangeli S, Tozzi A, et al. Is stereotactic body radiation therapy an attractive option for unresectable liver metastases? A preliminary report from a phase 2 trial. *Int. J. Radiat. Oncol. Biol. Phys* 2013;**86**(2):336–42, http://dx.doi.org/10.1016/j.ijrobp.2012.12.021.
7. Blomgren H, Lax I, Näslund I, Svanström 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, http://dx.doi.org/10.3109/02841869509127197.
8. Wulf J, Hädinger U, Oppitz U, Olshausen B, Flentje M. Stereotactic radiotherapy of extracranial targets: CT-simulation and accuracy of treatment in the stereotactic body frame. *Radiother. Oncol* 2000;**57**(2):225–36, http://dx.doi.org/10.1016/S0167-8140(00)00226-7.
9. Katz AW, Carey-Sampson M, Muhs AG, Milano MT, Schell MC, Okunieff P. Hypofractionated stereotactic body radiation therapy (SBRT) for limited hepatic metastases. *Int J Radiat Oncol* 2007;**67**(3):793–8, http://dx.doi.org/10.1016/j.ijrobp.2006.10.025.
10. Andratschke NH, Nieder C, Heppt F, Molls M, Zimmermann F. Stereotactic radiation therapy for liver metastases: factors affecting local control and survival. *Radiat Oncol* 2015;**10**(1), http://dx.doi.org/10.1186/s13014-015-0369-9.
11. Barney BM, Olivier KR, Miller RC, Haddock MG. Clinical outcomes and toxicity using Stereotactic Body Radiotherapy (SBRT) for advanced cholangiocarcinoma. *Radiat Oncol* 2012;**7**(1):67, http://dx.doi.org/10.1186/1748-717X-7-67.
12. Hoyer M, Roed H, Traberg Hansen A, et al. Phase II study on stereotactic body radiotherapy of colorectal metastases. *Acta Oncol (Madr)* 2006;**45**(7):823–30, http://dx.doi.org/10.1080/02841860600904854.
13. Kirkpatrick JP, Meyer JJ, Marks LB. The linear-quadratic model is inappropriate to model high dose per fraction effects in radiosurgery. *Semin. Radiat. Oncol* 2008;**18**(4):240–3, http://dx.doi.org/10.1016/j.semradonc.2008.04.005.
14. Song CW, Cho LC, Yuan J, Dusenbery KE, Griffin RJ, Levitt SH. Radiobiology of stereotactic body radiation therapy/stereotactic radiosurgery and the linear-quadratic model. *Int. J. Radiat. Oncol. Biol. Phys* 2013;**87**(1):18–9, http://dx.doi.org/10.1016/j.ijrobp.2013.03.013.
15. Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved? *Int. J. Radiat. Oncol. Biol. Phys* 2014;**88**(2):254–62, http://dx.doi.org/10.1016/j.ijrobp.2013.07.022.
16. Brenner DJ. The linear-quadratic model is an appropriate methodology for determining isoeffective doses at large doses per fraction. *Semin. Radiat. Oncol* 2008;**18**(4):234–9, http://dx.doi.org/10.1016/j.semradonc.2008.04.004.
17. Schefter TE, Kavanagh BD, Timmerman RD, Cardenes HR, Baron A, Gaspar LE. A Phase I trial of stereotactic body radiation therapy (SBRT) for liver metastases. *Int. J. Radiat. Oncol. Biol. Phys* 2005;**62**(5):1371–8, http://dx.doi.org/10.1016/j.ijrobp.2005.01.002.
18. McCammon R, Schefter TE, Gaspar LE, Zaemisch R, Gravdahl D, Kavanagh B. Observation of a dose-control relationship for lung and liver tumors after stereotactic body radiation therapy. *Int. J. Radiat. Oncol. Biol. Phys* 2009;**73**(1):112–8, http://dx.doi.org/10.1016/j.ijrobp.2008.03.062.
19. Chang DT, Swaminath A, Kozak M, et al. Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis. *Cancer* 2011;**117**(17):4060–9, http://dx.doi.org/10.1002/cncr.25997.
20. Mendez Romero A, Bakri L, Seppenwoolde Y, et al. Inter- and intraobserver variability in daily tumor setup using contrast-enhanced CT scans for patient positioning during stereotactic body radiation therapy for liver metastases. *Int J Radiat Oncol* 2013;**87**(2, Suppl.):S318, http://dx.doi.org/10.1016/j.ijrobp.2013.06.836.
21. Boda-Heggemann J, Dinter D, Weiss C, et al. Hypofractionated image-guided breath-hold SABR (Stereotactic Ablative Body

Radiotherapy) of liver metastases – clinical results. *Radiat Oncol* 2012;**7**(1):92, http://dx.doi.org/10.1186/1748-717X-7-92.
22. Kavanagh BD, Schefter TE, Cardenes HR, et al. Interim analysis of a prospective phase I/II trial of SBRT for liver metastases. *Acta Oncol (Madr)* 2006;**45**(7):848–55, http://dx.doi.org/10.1080/02841860600904870.
23. Høyer M, Swaminath A, Bydder S, et al. Radiotherapy for liver metastases: a review of evidence. *Int. J. Radiat. Oncol. Biol. Phys* 2012;**82**(3):1047–57, http://dx.doi.org/10.1016/j.ijrobp.2011.07.020.
24. Klein J, Dawson La. Hepatocellular carcinoma radiation therapy: review of evidence and future opportunities. *Int. J. Radiat. Oncol. Biol. Phys* 2013;**87**(1):22–32, http://dx.doi.org/10.1016/j.ijrobp.2012.08.043.
25. Lee MT, Kim JJ, Dinniwell R, et al. Phase i study of individualized stereotactic body radiotherapy of liver metastases. *J. Clin. Oncol* 2009;**27**(10):1585–91, http://dx.doi.org/10.1200/JCO.2008.20.0600.
26. Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J. Clin. Oncol* 2009;**27**(10):1572–8, http://dx.doi.org/10.1200/JCO.2008.19.6329.
27. Goodman Ka, Wiegner EA, Maturen KE, et al. Dose-escalation study of single-fraction stereotactic body radiotherapy for liver malignancies. *Int. J. Radiat. Oncol. Biol. Phys* 2010;**78**(2):486–93, http://dx.doi.org/10.1016/j.ijrobp.2009.08.020.
28. 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, http://dx.doi.org/10.1200/JCO.2007.14.3529.
29. Guha C, Kavanagh BD. Hepatic radiation toxicity: avoidance and amelioration. *Semin. Radiat. Oncol* 2011;**21**(4):256–63, http://dx.doi.org/10.1016/j.semradonc.2011.05.003.
30. De Bari B, Guillet M, Mornex F. Radiothérapie en conditions stéréotaxiques des métastases hépatiques. *Cancer/Radiothérapie* 2011;**15**(1):72–6, http://dx.doi.org/10.1016/j.canrad.2010.11.005.
31. Pan CC, Kavanagh BD, Dawson La, et al. Radiation-associated liver injury. *Int. J. Radiat. Oncol. Biol. Phys* 2010;**76**(3, Suppl.):94–100, http://dx.doi.org/10.1016/j.ijrobp.2009.06.092.
32. Thomas TO, Hasan S, Small W, et al. The tolerance of gastrointestinal organs to stereotactic body radiation therapy: what do we know so far? *J Gastrointest Oncol* 2014;**5**(3):236–46, http://dx.doi.org/10.3978/j.issn.2078-6891.2014.024.
33. Murphy JD, Hattangadi-Gluth J, Song WY, et al. Liver toxicity prediction with stereotactic body radiation therapy: the impact of accounting for fraction size. *Pract Radiat Oncol* 2014;**4**(6):372–7, http://dx.doi.org/10.1016/j.prro.2013.12.004.
34. De Bari B, Pointreau Y, Rio E, Mirabel X, Mornex F. Dose de tolérance à l'irradiation des tissus sains: le foie. *Cancer/Radiothérapie* 2010;**14**(4–5):344–9, http://dx.doi.org/10.1016/j.canrad.2010.02.013.
35. Sanuki N, Takeda A, Oku Y, et al. Threshold doses for focal liver reaction after stereotactic ablative body radiation therapy for small hepatocellular carcinoma depend on liver function: evaluation on magnetic resonance imaging with Gd-EOB-DTPA. *Int. J. Radiat. Oncol. Biol. Phys* 2014;**88**(2):306–11, http://dx.doi.org/10.1016/j.ijrobp.2013.10.045.
36. Timmerman RD, Herman J, Cho LC. Emergence of stereotactic body radiation therapy and its impact on current and future clinical practice. *J. Clin. Oncol* 2014;**32**(26), http://dx.doi.org/10.1200/JCO.2014.55.4675.
37. Osmundson EC, Wu Y, Luxton G, Bazan JG, Koong AC, Chang DT. Predictors of toxicity associated with stereotactic body radiation therapy to the central hepatobiliary tract. *Int J Radiat Oncol* 2015;**91**(5):986–94, http://dx.doi.org/10.1016/j.ijrobp.2014.11.028.
38. Andolino DL, Forquer JA, Henderson MA, et al. Chest wall toxicity after stereotactic body radiotherapy for malignant lesions of the lung and liver. *Int. J. Radiat. Oncol. Biol. Phys* 2011;**80**(3):692–7, http://dx.doi.org/10.1016/j.ijrobp.2010.03.020.
39. Dawson LA, Normolle D, Balter JM, McGinn CJ, Lawrence TS, Ten Haken RK. Analysis of radiation-induced liver disease using the Lyman NTCP model. *Int. J. Radiat. Oncol. Biol. Phys* 2015;**53**(4):810–21, http://dx.doi.org/10.1016/S0360-3016(02)02846-8.
40. Dawson La, Normolle D, Balter JM, McGinn CJ, Lawrence TS, Ten Haken RK. Analysis of radiation-induced liver disease using the Lyman NTCP model. *Int. J. Radiat. Oncol. Biol. Phys* 2002;**53**(4):810–21, http://dx.doi.org/10.1016/S0360-3016(02)02846-8.
41. Andolino DL, Johnson CS, Maluccio M, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. *Int. J. Radiat. Oncol. Biol. Phys* 2011;**81**(4):447–53, http://dx.doi.org/10.1016/j.ijrobp.2011.04.011.
42. Eriguchi T, Takeda a, Oku Y, et al. Multi-institutional comparison of treatment planning using stereotactic ablative body radiotherapy for hepatocellular carcinoma – benchmark for a prospective multi-institutional study. *Radiat Oncol* 2013;**8**:113, pii:1748-717X-8-113, doi:r10.1186/1748-717X-8-113.
43. Kopek N, Holt MI, Hansen AT, Hoyer M. Stereotactic body radiotherapy for unresectable cholangiocarcinoma. *Radiother. Oncol* 2010;**94**(1):47–52.
44. Hoyer M, Roed H, Sengelov L, et al. Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. *Radiother. Oncol* 2005;**76**(1), http://dx.doi.org/10.1016/j.radonc.2004.12.022.
45. Bae SH, Kim M-S, Cho CK, et al. Predictor of severe gastroduodenal toxicity after stereotactic body radiotherapy for abdominopelvic malignancies. *Int. J. Radiat. Oncol. Biol. Phys* 2012;**84**(4):e469–74, http://dx.doi.org/10.1016/j.ijrobp.2012.06.005.
46. Méndez 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, http://dx.doi.org/10.1080/02841860600897934.
47. Kirkpatrick JP, Kelsey CR, Palta M, et al. Stereotactic body radiotherapy: a critical review for nonradiation oncologists. *Cancer* 2014;**120**(7):942–54, http://dx.doi.org/10.1002/cncr.28515.