Acta Oncologica, 2012; 51: 568–574

informa
healthcare

INVITED ARTICLE

An international survey on liver metastases radiotherapy

MICHAEL I. LOCK[1], MORTEN HOYER[2], SEAN A. BYDDER[3], PAUL OKUNIEFF[4], CAROL A. HAHN[5], ANUSHREE VICHARE[6] & LAURA A. DAWSON[7]

[1]*Department of Radiation Oncology, University of Western Ontario, London, Ontario, Canada,* [2]*Department of Oncology, Aarhus University Hospital, Aarhus, Denmark,* [3]*Radiation Oncology, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia,* [4]*Department of Radiation Oncology, University of Florida, Gainesville, Florida, USA,* [5]*Department of Radiation Oncology, Duke University Medical Center, Raleigh, North Carolina, USA,* [6]*American Society of Radiation Oncology, Fairfax, Virginia, USA and* [7]*Radiation Medicine Program, Princess Margaret Hospital, Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada*

Abstract

Background. An international survey of radiation therapy (RT) of liver metastases was undertaken by the Liver Cancer Workgroup of the Third International Consensus on Metastases Workshop at the 2010 American Society for Radiation Oncology (ASTRO) meeting. *Material and methods*. Canadian, European, Australian, New Zealand and American centers participated in this online survey. The survey had four objectives: 1) to describe the practice patterns for RT of liver metastases; 2) to report on the use of low-dose RT for symptomatic liver metastases; 3) to report on the use of technology; and 4) to describe the regional differences in the management of liver metastases. *Results.* A total of 69 individuals treating liver metastases with radiotherapy responded to the survey. Regional response rates ranged from 39% to 50%. The primary professional affiliation of all respondents was evenly distributed amongst ASTRO, CARO, ESTRO and TROG/RANZCR. A 36% increase in the average annual number of referrals over the past five years is reported. The majority of referrals were for radical RT. The most common technologies used were 4D-CT (61%), SBRT (55%), IGRT (50%), and/or IMRT (28%). A uniform treatment approach was not found. The most commonly employed radical regimens were 45 Gy in 3 fractions, 40–50 Gy in 5 fractions, and 45 Gy in 15 fractions. Palliative regimens included 20 Gy in 5 fractions, 30 Gy in 10 fractions, 8 Gy in 1 fraction, and 10 Gy in 2 fractions. *Conclusions*. This survey suggests radiation oncologists will be seeing more referrals for liver RT. The majority of experience in liver metastases RT is with radical SBRT for focal metastases rather than low-dose palliative RT for symptom control. There is significant variation in technology utilization and dose regimens. Prospective studies or registries may allow for comparison of regimens and identification of parameters to optimize patient selection.

The liver is a common site of metastases for cancers such as colorectal, lung and breast [1]. In the past, patients with liver metastases were thought to have a dire prognosis and the value of any treatment was debated [2]. However, patients have a spectrum of clinical presentations, from potentially curable (e.g. isolated liver metastases from colorectal carcinoma) to end-stage with limited survival (e.g. diffuse symptomatic liver metastases from lung cancer) motivating the search for improved patient selection and treatments for these patients. Radiation therapy offers the potential for cure in the setting of oligometastases [3] and palliation of symptoms in the setting of diffuse disease [4].

Currently there is no consensus on the most appropriate selection of patients for RT, use of technology, or the ideal RT management strategy. No randomized controlled studies examining the benefit of external beam RT for liver metastases have been published. Indeed there is a general lack of level I evidence for essentially all local liver treatments other than surgery [5]. The lack of level I evidence and the risks of whole liver radiation [6] have led to a slow and non-uniform adoption of RT for the treatment of liver metastases. Several consensus documents have been published on liver metastases [7–11]. However, all were primarily driven by non-radiotherapy disciplines and focus on surgical and chemotherapeutic

Correspondence: M. I. Lock, A3-910, Department of Radiation Oncology, London Regional Cancer Program, London Health Sciences Centre, 790 Commissioners Rd East, London, Ontario N6A 4L6, Canada. Tel: +1 519 685 8500 ext 53347. Fax: +1 519 685 8736. E-mail: Michael.Lock@lhsc.on.ca

(Received 27 February 2012; accepted 22 March 2012)

ISSN 0284-186X print/ISSN 1651-226X online © 2012 Informa Healthcare
DOI: 10.3109/0284186X.2012.681700

options. This paper is the first published international survey regarding the role of RT for the treatment of liver metastases, for palliation of symptoms and also for potentially ablative therapy.

At the Third International Consensus Conference on Palliative Radiotherapy held at the American Society for Radiation Oncology (ASTRO) 52nd Annual Meeting 2010, five working groups were set up in the following sites: liver metastases, brain metastases, bone metastases, palliative lung and spinal cord compression. Members of the Liver Metastases Consensus Group were appointed by the ASTRO, the European Society for Therapeutic Radiology and Oncology (ESTRO), the Canadian Association of Radiation Oncology (CARO) and the Trans-Tasman Radiation Oncology Group (TROG). This working group was commissioned to survey the current practice patterns and identify areas for research for radiotherapy (RT) of liver metastases. The purpose of this paper is to disseminate the results of this international survey. The survey formed the background for the development of an evidenced-based review that has been published separately [12].

Material and methods

In Canada, New Zealand, Australia and Europe, respondents representing centers that treat liver cancer were identified. Centers were canvassed to identify individuals who could represent each center. For example, in Canada, a letter was sent to each center requesting whether liver lesions were treated and, if so, to identify an appropriate respondent. In addition, respondents were identified by an author search in Pubmed (MESH headings liver, hepatic, radiation) and a review of conference proceedings. This targeted method minimized selection bias by avoiding possibilities such as obtaining multiple responses from several oncologists in a center performing a large number of liver treatments. Centers without experience in liver radiation were excluded from the survey. In the US, a targeted survey was not possible and a general survey was circulated to all ASTRO members. Data was stratified by country and professional membership to assess for possible bias in responses caused by the selection method.

The survey consisted of four sections focusing on respondent demographics, patient demographics, technology and techniques utilized, and a review of active research in RT for liver metastases. A modified Dillman survey technique was used [13]. This response maximizing technique consisted of notifying possible respondents through professional organization newsletters of the pending survey. Surveys were then digitally sent out followed by a reminder and a final email. This survey was performed in conjunction with the non-targeted brain metastases and spinal cord compression surveys, as well as targeted lung and bone metastases endpoint surveys. The online surveys were available for a period of three months ending June 30, 2010. No incentive was offered for participation. Since the respondents were able to select multiple answers for certain questions, the total percentage (percent of cases) does not add up to a 100% for selected questions. Missing responses were not imputed and were not included in the corresponding analysis. SPSS 17.0 statistical package was used for analysis. Descriptive analysis was used to compute frequencies and percentages. Statistical comparisons were made using contingency tables and χ^2 statistics. Statistical analyses were not reported where more than 20% of cells had a count less than 5. All tests of significance were two-sided and statistical differences were considered significant at p-values less than 0.05.

Results

Respondent characteristics

A total of 80 individuals responded to the survey. Eleven respondents who did not treat liver metastases were excluded; therefore, 69 respondents were entered into the analysis. Response rates varied from 39% (New Zealand and Australia) to 50% (Canada). The US response rate is not reported as this group received a general survey to all members without specific targeting to centers with experience in treating liver metastases. An overall response rate cannot be determined as the denominator, number of sites treating liver metastases, is unknown. The primary oncology membership was as follows: ESTRO 26%, ASTRO 25%, CARO 23%, TROG/RANZCR (Royal Australian and New Zealand College of Radiologists) 19% and other 7%. The primary country of practice was Europe 32%, US 20%, Canada 25%, Australia/New Zealand 19% and other countries 4%.

The respondent demographics are summarized in Table I. Approximately 60% of respondents have been treating liver metastases for less than 10 years with most treating liver metastases only in the last four years. Forty-six percent were in an academic or university practice and the majority (88%) were from a hospital-based practice versus freestanding centers. The average number of radiation oncologists at treating centers was 11 with a median of eight (range, 1–40). In terms of multidisciplinary support 65% had a multidisciplinary gastrointestinal and/or a liver tumor board available in their center.

Most respondents have noted a significant increase in referrals for liver metastases. Five years prior to the survey, respondents indicated that they saw an average of 13 patients per year with liver cancers, which increased to 20 in the last calendar year of the survey, representing a 54% increase. There was a divergence of responses as to how many of the referred patients were treated. Overall, 38% of respondents indicated that they treat a majority of their referred patients (defined as more than 75% of referred patients). However, this varied from 15% to 70% by country. The US and Europe tended to treat a higher percentage of referred patients than Canada, Australia and New Zealand.

Patient demographics and management alternatives

A majority of the referrals were for radical RT/SBRT as opposed to palliative low-dose RT. Relative and absolute contraindications to liver RT according to respondents are listed in Figure 1. There was stronger agreement on relative contraindications to treatment, with a majority (>70%) of respondents selecting cirrhosis and Child-Pugh class. Agreement on absolute contraindications was more varied. In terms of management alternatives, nearly all had access to hepatobiliary surgery (91%), transcatheter arterial chemoembolization (66%) and radiofrequency ablation (89%). Fewer had access to hepatic arterial radioembolization (yttrium-90) (23%) or radiolabelled I131 lipiodol (18%).

Technology, regimens and techniques

For palliative intent symptom control, we asked what was the most commonly offered dose fractionation. Over 90% of respondents used four fractionations: 8 Gy in 1 fraction (24%), 10 Gy in 2 fractions (11%), 20 Gy in 5 fractions (30%), and 30 Gy in 10 fractions (17%) [Supplementary Table Ib available online at http//www.informahealthcare.com/doi/abs/10.3109/0284186X.2012.681700]. The dose regimens varied by country of primary practice and membership affiliation. The data indicate that ASTRO and CARO responders tend to use higher biologically effective dose (BED) regimens for palliative intent symptom management. For example, only 23% of ASTRO and CARO responders used lower BED fractionations (defined as BED <15 Gy regimens such as 30 Gy in 10 fractions and 10 Gy in 2 fractions) compared to 50% of TROG/RANZCR and ESTRO responders. There were no questions on the volumes irradiated.

This survey asked specific questions to address the use of technologies such as SBRT. Half of the respondents offered SBRT for the treatment of liver metastases. Overall, 50% and 28% of respondents used IGRT and IMRT, respectively. Terms such as IGRT, IMRT and SBRT were not defined by the surveyors. There was a wide range of dose fractionation schedules used for radical treatment. The three most common regimens used were: 45 Gy in 3 fractions (23%), 45 Gy in 15 fractions (10%), and 40–50 Gy in 5 fractions (15%) [Supplementary Table Ia available online at http//www.informahealthcare.com/doi/abs/10.3109/0284186X.2012.681700]. Other fractionations included 50 Gy in 20 fractions, 60 Gy in 30 fractions, and 36–54 Gy in 6 fractions. BED ranged from 14 Gy to 180 Gy. A large proportion of centers (28%) used 'other' doses including individualized dosing regimens specific to each patient.

In regards to post-operative RT for liver metastases, 64% of those surveyed would not offer RT. Of the 36% that would offer treatment, the most commonly used regimen was 60 Gy in 30 (29%). Alternatives listed by respondents included 50 Gy in 20 fractions, 45 Gy in 15 fractions and 40–50 Gy in 5 fractions (with a BED range from 59 Gy to 113 Gy).

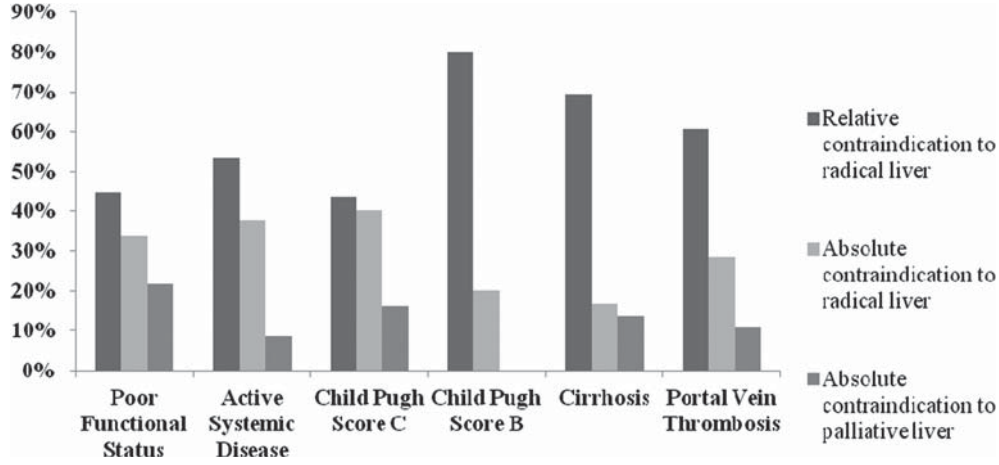

Figure 1. Contraindications to liver radiation.

Table I. Respondent demographics.

Regional/country of practice (n = 69)	
Europe	22 (32%)
Australia/New Zealand	13 (19%)
United States of America	14 (20%)
Canada	17 (25%)
Other	3 (4%)
Primary oncology membership (n = 69)	
ASTRO	17 (25%)
ESTRO	18 (26%)
CARO	16 (23%)
TROG/RANZCR	13 (19%)
OTHER	5 (7%)
Year of completion of training (n = 69)	
≤ 1985	7 (10%)
1986–1990	10 (14%)
1991–1995	13 (19%)
1996–2000	18 (26%)
2001–2005	13 (19%)
2006–2012	8 (12%)
Type of practice (n = 69) *Multiple response options	
Directly government funded	21 (26%)
Private practice	22 (28%)
Academic/University	37 (46%)
Type of primary practice setting (n = 69)	
Hospital based	61 (88%)
Free-standing	8 (12%)
Type of reimbursement received (n = 69)	
Fee-for-service	14 (20%)
Salary	41 (59%)
Both	11 (16%)
Other	3 (4%)
Years of treating liver cancer (n = 69)	
0–4	25 (36%)
5–9	16 (23%)
10–14	8 (12%)
15–19	11 (16%)
20 or more	9 (13)

The use of advanced technologies in radical intent RT for liver metastases varied between regions and by primary professional affiliation (a Supplementary Figure 1 comparing the use of technology by professional affiliation is available online at http//www.informahealthcare.com/doi/abs/10.3109/0284186X.2012.681700). Differences in IGRT were statistically significant (p = 0.004): US (90%), Europe (55%), Canada (42%), Australia/New Zealand (9%). SBRT was used by 83% and 91% of ASTRO and ESTRO respondents, respectively. This is compared to 42% of CARO and none of the TROG/RANZCR respondents. Use of specialized tools for RT planning and delivery included respiratory gating at simulation (58%), respiratory gating during treatment (38%), active breathing control (13%), arc therapy (20%), individualized dose regimens (57.5%) and radiobiological guidance (15%). There were 12 respondents who offered radioembolization (hepatic arterial yttrium-90), I131 lipiodol, and/or interstitial brachytherapy for patients with liver metastases.

Research

Twenty-six percent of patients were on prospective trials with ESTRO members having disproportionately more patients on trials (46% compared to the next highest professional group, CARO, with 26% on trial). ASTRO respondents indicated that 8% of their patients were on trial. According to the survey, three centers were participating in a phase III trial. Only 33% of respondents maintained a database of liver RT outside of a trial.

In regards to low-dose radiation for symptomatic management, a majority of centers reported referrals of four or less patients per year [Supplementary Figure 2a addresses the number of referrals per year is available online at http//www.informahealthcare.com/doi/abs/10.3109/0284186X.2012.681700]. If a trial was available, most centers (68%) indicated that referrals would likely double. A breakdown by number of patients referred, with and without a trial, is provided in figures 2A and 2B found online at http//www.informahealthcare.com/doi/abs/ 10.3109/0284186X.2012.681700. A trial comparing steroids with or without low-dose palliative radiation would be supported by 77% of respondents. This result varied by professional membership affiliation. Support for such a palliative liver RT trial was low from ASTRO (40%) versus a high level of support from the other professional groups (85–90%).

Discussion

The management of liver metastases is an increasingly significant oncologic problem worldwide [2,3]. Control of liver metastases from some primary cancers, such as colorectal carcinoma, has an important impact on disease-free survival and overall survival [14]. Indeed, the likelihood of dying is almost tripled for patients with liver metastases [15] compared to those with metastatic cancer without liver metastases. If untreated, patients with liver metastases typically have a reported survival of less than 6% at one year [14]. Therefore, identification of improved treatments is an important unmet need for our patients. Where high level evidence is not available, the collection of data through surveys and combined databases plays an important role in the effort to determine best practice. There have been several national surveys and patterns of care studies reported in the literature for palliative RT [16,17]. However, the present work is the first international survey addressing the use of palliative RT for liver metastases.

This survey confirms that the variation in global liver RT patterns of practice is substantial. The fact that patients receive different treatments based on the center and/or professional affiliation of the consulting physician may translate into sub-optimal outcomes. Providing uniform referral recommendations

and informing patients of the benefits and risks of RT is made extremely difficult if the treatment and technology is varied. For example, there was a notable variation in the use of 4D-CT. 4D-CT was used by 82% of ESTRO respondents compared to 30% of TROG/RANZCR respondents. 4D-CT studies, such as Wagman's study on liver tumors from Memorial Sloan Kettering [18], demonstrate the value of gating in margin reduction and, in turn, dose escalation. Wagman's study suggests this variation in practice may have a direct impact on clinical outcomes, such as toxicity, if ablative doses are to be used. Furthermore, the use of IGRT [a Supplementary Figure 1 demonstrating the differences in technology utilization by professional affiliation is available online at http//www.informahealthcare.com/doi/abs/10.3109/0284186X.2012.681700], arguably a critical quality assurance mechanism in liver treatment, was statistically different between regions with utilization as low as 9%. The AAPM Task Group 101 recommends a patient-specific tumor-motion assessment for all SBRT patients and image guidance with targets within the abdomen [19]. Although it is possible that some of the variation in responses could be due to the lack of specific technology definitions in the survey, the wide variation may more likely be explained by a variance in technology acquisition, implementation and/or experience. This data should encourage re-evaluation of institutional protocols, development of guidelines, and participation in trials to decrease variation in the use of technology.

This wide variation in RT management will lead to a variation in publications describing the potential value and toxicity of radiation. Patients and referring health care providers may be confused by the differing techniques, indications and published outcomes. This hypothesis is supported by the survey results indicating that the referral rate varies substantially by region. For example, 53% of European respondents indicated receiving more than 20 referrals per year for hepatic metastases compared to only 20% of Australian/New Zealand and US respondents. This may be due to a lack of evidence and a need for the radiation oncology community to develop uniform guidelines to assist referring physicians and patients searching for treatment options.

Improved selection of patients with metastases who will benefit from local therapy is also needed. In our survey, there was no clear consensus on contraindications to liver RT (Figure 1). In terms of absolute contraindications, Child-Pugh class C and poor functional status were commonly selected. Relative contraindications included cirrhosis, portal vein thrombosis and Child-Pugh class B. Although it is established that radiation induced liver toxicity is more likely in patients with impaired liver function (Child-Pugh B or C), the literature demonstrates that RT can be used safely in many patients with cirrhosis and malignant thrombosis when certain dosimetric parameters are met [20–22]. Indeed, portal vein thrombosis need not be a relative contraindication to liver RT and may be an indication for treatment [23]. Recent overview publications propose practical parameters that may be helpful in patient selection including specifics on the proximity to luminal gastrointestinal tissues and the volume of residual functional liver [24].

Patients presenting with symptomatic diffuse liver metastases, regardless of liver function, may receive palliative benefits from low-dose RT. We wanted to gauge the international interest in a trial for this subpopulation. Low-dose local RT has long been used for palliation of symptoms from metastases at many sites (i.e. bone, brain) with success. Several studies have demonstrated that low dose RT can provide significant palliation of symptoms [25]. Bydder et al. assessed 10 Gy in 2 fractions to partial or whole liver and reported that at two weeks, response rates were 53–66%. Fifty-four percent experienced partial or complete global symptomatic responses [4]. However, there was a 7% grade 3 toxicity rate and a 14% temporary exacerbation in pain. In our survey, referrals for palliative liver RT were comparatively low (a median of two patients referred per year with a range 0 to 60). This data was consistently reported from all countries. Respondents suggested that referral rates would double if a trial were available. Furthermore, there was strong support for a clinical trial with 77% of the respondents indicating a willingness to participate in a randomized trial of steroids with or without low-dose palliative RT trial if available. However, the willingness to participate in a trial varied by primary professional affiliation. Members of CARO, ESTRO and TROG/RANZCR supported a randomized trial in low-dose radiation according to over 85% of respondents. However, only 42% of those with ASTRO membership supported such a trial. A possible explanation for this variation may be the finding of a greater routine use of radical SBRT treatments by ASTRO members. Although there was some variability in dose and use of low-dose palliative RT for symptom control, respondents agreed with a simple strategy for testing this question. This highlights the need for further investigation in this subpopulation. A multicenter clinical trial is being developed to address this issue. In this study, a low dose may be delivered to the whole liver safely (8 Gy in 1 fraction) compared to steroids and best supportive care only.

This practice survey, along with an international review of the evidence for liver metastases by the Liver Cancer Workgroup [12], highlights the specific

questions in need of research and discussion. Fundamental questions include which patients are appropriate for liver RT, what is the most appropriate dose fractionation regimen, how should treatment modalities be sequenced, and what techniques and parameters are necessary to treat these patients safely? This international survey can provide a baseline for future comparisons and a method to identify areas requiring additional research. Furthermore, areas where treatment in the survey differs from a center's standard of care can serve to assist caregivers in improving their practice. As these questions are addressed, hopefully a greater consistency of practice will emerge that will lead to better outcomes for our patients and greater participation in clinical trials.

There are several limitations of this paper. First, there was a variation in the method used to select respondents. In Canada, Australia, New Zealand and Europe, we were able to identify a single representative from each center. In the US, individual center representatives could not be identified and the denominator consisted of a broad email out to all ASTRO members. Reporting on overall responses may be misleading and differences may be related to the method of selection. As the Australian, New Zealand, Canadian and European surveys were targeted to oncologists known to treat liver lesions, these respondents may have an increased interest and knowledge of liver radiotherapy compared to the general survey to the US. The weakness of the non-targeted survey is that a large institution may have more responders and may skew the data to their practice pattern. Furthermore, a non-targeted survey may include respondents who are less experienced thereby introducing greater variability in responses. We did compare number of years in practice, size of center, years treating liver patients and number of liver metastases patients seen per year; no clear difference by region or affiliation was noted. This suggests that this methodology did not introduce increased variability. However, to address this issue, areas of consistency and inconsistency by region and professional affiliation are highlighted within this document. Lastly, the management of liver lesions is evolving rapidly. Some of the data collected may no longer accurately reflect the current practice pattern. For example, the use of technologies such as 4D-CT, IGRT and SBRT may have become more widely available in various countries. In addition, there is a learning curve with new technology that may have contributed to some variability in response.

This international survey represents a snapshot of practice by geography and professional affiliation. The survey identifies principle areas of variation and improvement, realizing that not all centers have the same resources. The majority of experience in liver metastases RT is with SBRT for focal metastases compared to low-dose palliative RT. Many oncologists have only recently started to treat liver lesions with RT and the referral rates are increasing. There is a wide variation in the utilization of technology, but a majority of centers have the fundamental tools in place. However, tools such as IGRT and 4D-CT, arguably critical to achieve an appropriate therapeutic ratio for liver SBRT, are under utilized. A wide variation of treatment regimens and treatment intent was also observed; this suggests that these are the specific areas requiring guidance that would benefit from focused collaborative research. In addition, there was a wide range of referral rate between centers indicating that referring physicians are also not clear about the indications for RT. These variations suggest to the authors that an expert consensus and clinical trials are needed to provide guidance to referring physicians and radiation oncologists if radiation oncology is to establish itself as an accepted treatment modality in this area.

Acknowledgements

The authors would like to thank Shari Siuta and Sidrah Abdul for administrative support during the conduct of this project.

Declaration of interest: The following authors have conflicts of interests that may pertain to the content of this manuscript. LD holds a grant from Bayer. MH receives a research grant from Varian Medical Systems and the Lundbeck Centre for Interventional Research in Radiation Oncology (CIRRO).

References

[1] Hess KR, Varadhachary GR, Taylor SH, Wei W, Raber MN, Lenzi R, et al. Metastatic patterns in adenocarcinoma. Cancer 2006;106:1624–33.

[2] Nordlinger B, Rougier P. Liver metastases from colorectal cancer: The turning point. J Clin Oncol 2002;20:1442–5.

[3] Lo SS, Moffatt-Bruce SD, Dawson LA, Schwarz RE, Teh BS, Mayr NA, et al. The role of local therapy in the management of lung and liver oligometastases. Nat Rev Clin Oncol 2011;8:405–16.

[4] Bydder S, Spry NA, Christie DR, Roos D, Burmeister BH, Krawitz H, et al. A prospective trial of short-fractionation radiotherapy for the palliation of liver metastases. Australas Radiol 2003;47:284–8.

[5] Al-Asfoor A, Fedorowicz Z, Lodge M. Resection versus no intervention or other surgical intervention for colorectal cancer liver metastases. Cochrane Database Syst Rev. 2008; 16:CD006039.

[6] 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;27:117–23.
[7] Vickers M, Samson B, Colwell B, Cripps C, Jalink D, El-Sayed S, et al. Eastern Canadian Colorectal Cancer Consensus Conference: Setting the limits of resectable disease. Curr Oncol 2010;17:70–7.
[8] Van Cutsem E., Nordlinger B. Advanced colorectal cancer: ESMO clinical practice guidelines for treatment. Ann Oncol 2010;21(Suppl 5):v93–7.
[9] Abdalla EK, Adam R, Bilchik AJ, Jaeck D, Vauthey JN, Mahvi D. Improving resectability of hepatic colorectal metastases: Expert consensus statement. Ann Surg Oncol 2006;13: 1271–80.
[10] Nordlinger B, Van Cutsem E, Gruenberger T, Glimelius B, Poston G, Rougier P, et al. Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: Recommendations from an expert panel. Ann Oncol 2009;20:985–92.
[11] Berry S, Law C, Vuong T, Chen E, Cripps C, Maroun J, et al. Standards of care for curative surgery and management of metastatic colorectal cancer: Report form the Colorectal Cancer Association of Canada Consensus meeting. Oncol Exchange 2011;10:15–20.
[12] Hoyer M, Swaminath A, Bydder S, Lock M, Mendez Romero A, Kavanagh B, et al. Radiotherapy for liver metastases: A review of evidence. Int J Radiat Oncol Biol Phys 2012;82: 1047–57.
[13] Dillman D. Mail and telephone surveys. The total design method. 1st ed. New York: Wiley; 1978.
[14] Wood CB, Gillis CR, Blumgart LH. A retrospective study of the natural history of patients with liver metastases from colorectal cancer. Clin Oncol 1976;2:285–8.
[15] Vigano A, Donaldson N, Higginson IJ, Bruera E, Mahmud S, Suarez-Almazor M. Quality of life and survival prediction in terminal cancer patients. A multicenter study. Cancer 2004;101:1090–8.
[16] Fairchild A, Barnes E, Ghosh S, Ben-Josef E, Roos D, Hartsell W, et al. International patterns of practice in palliative radiotherapy for painful bone metastases: Evidenced based practice? Int J Radiat Oncol Biol Phys 2009;75: 1501–10.
[17] McCloskey SA, Tao ML, Rose CM, Fink A, Amadeo AM. National survey of perspectives of palliative radiation therapy: Role, barriers, and needs. Cancer J 2007;13:130–7.
[18] Wagman R, Youke E, Ford E, Giraud P, Mageras G, Minsky B, et al. Respiratory gating for liver tumors: Use in dose escalation. Int J Radiat Oncol Biol Phys 2003;55: 659–68.
[19] Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, et al. Stereotactic body radiation therapy: The report of AAPM Task Group 101. Med Phys 2010; 37:4078–101.
[20] Schefter TE, Kavanagh BD. Radiation therapy for liver metastases. Semin Radiat Oncol 2011;21:264–70.
[21] Guha C, Kavanagh BD. Hepatic radiation toxicity: Avoidance and amelioration. Semin Radiat Oncol 2011;21: 256–63.
[22] Zeng ZC, Fan J, Tang ZY, Zhou J, Qin LX, Wang JH, et al. A comparison of treatment combinations with and without radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombus. In J Radiat Oncol Biol Phys 2005;61:432–43.
[23] Minagawa M, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein thrombus. World J Gastroenterol 2006;12:7561–7.
[24] Dawson LA. Overview: Where does radiation therapy fit in the spectrum of liver cancer local-regional therapies? Semin Radiat Oncol 2011;21:241–6.
[25] Greco C, Catalano G, Di Grazia A, Orecchia R. Radiotherapy of liver malignancies. From whole liver irradiation to stereotactic hypofractionated radiotherapy. Tumori 2004; 90:73–9.

Supplementary material available online

Supplementary Table Ia and Ib, Figures 1 and 2. Available online at http://www.informahealthcare.com/doi/abs/10.3109/0284186X.2012.681700.