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Editorial

1. Stereotactic body radiation therapy for liver tumors

Liver tumors (both primary and metastatic) are becoming increasingly common and an appropriate management is needed. This was the main subject of the XXI GOCO (Grup d'Oncologia Català i Occità) meeting held in Montpellier, France in October 2013, where a number of interesting presentations about multimodality management of liver cancer gave place to this special issue.

For medically operable patients with resectable disease, surgery remains the standard of treatment. For patients who are not candidates for surgery other local treatments exist and include Stereotactic body radiotherapy (SBRT). SBRT is a new radiation treatment method to deliver with high accuracy a high dose of radiation to small and well-defined targets, utilizing either a single dose or a small number of fractions with a high degree of precision within the body.[1] Recent advances in imaging technologies allow a precise location of the target volume and to take into account tumor motion during the respiratory cycle. In addition, improved patient immobilization systems and new maneuvers to control the movement of the target volume allow the minimization of margins. Because of all these advances along with the refinement of planning systems and the possibility to use different imaging modalities, it is now possible to deliver an ablative radiation dose to small and well-defined targets in one or a few fractions resulting in a high biological effective dose.

SBRT is being investigated in the initial treatment of some primary[2,3] and secondary malignant tumors[4] and in the reirradiation situation.[5] Initial clinical experiences with SBRT show impressive results with high local control and low toxicity rates in most tumor locations studied. Although there is an active clinical research with encouraging results (and a significant increase in the number of publications in recent years), there are still no clear indications for the use of SBRT, except for patients unfit for surgery, diagnosed with early stage non-small cell lung cancer. Retrospective and prospective phase II trials show generally good and encouraging clinical results but randomized phase III trials are needed to confirm and to evidence the therapeutic potential of SBRT.

This special issue is entirely dedicated to SBRT for liver tumors. Eight articles are fundamentally clinical, five focus on technical aspects of hepatic surgery, non-surgical treatments and liver SBRT and one paper review the radiobiology of high doses of radiation on tumor and normal tissues.

As mentioned above, surgery remains the most common and first-line standard treatment for primary hepatic cancer and liver metastasis. In the case of liver metastasis, hepatic resection is safe and effective obtaining good results with 5 years survival between 25 and 40% not only in colorectal metastasis but also in noncolorectal hepatic dissemination.[6,7] Unfortunately, only a small proportion (20–25%) of patients with liver metastasis are candidate for surgical resection, mainly due to bad general condition and comorbidities, extent of disease or poor hepatic reserve. Suc et al. described technical aspects of liver surgery and discussed the place and indications of SBRT from the surgical point of view. They highlight the importance of discussing all patients with malignant liver tumors in a multidisciplinary committee to decide the best treatment strategy for the patient including the combination of local therapies, as well as the participation of radiation oncologist in the multidisciplinary meetings.[8]

Revel-Mouroz et al. reviewed the technical aspects of non-surgical treatments for liver tumors (endovascular treatments and direct transcapsular access) offered by interventional radiology and therapeutic indications. Besides being effective and minimally invasive, they can be used in combined treatment strategies.[9]

Two papers from Montpellier focused on technical aspects of hepatic SBRT. Riou et al. critically discuss the minimum requirements and ideal technique for liver metastasis SBRT planning.[10]

In a very well done and documented study, Bedos et al. evaluated the reproducibility of tumor repositioning during gated volumetric-modulated arc therapy for liver SBRT using implanted fiducial markers and intrafraction imaging. A total of 2705 intrafraction images were retrospectively analyzed in 10 patients to assess the differences between expected and actual positions of fiducial markers along the cranio-caudal axis during the exhalation phase that is the most reproducible phase. They found a mean absolute intrafraction fiducial marker deviation along the cranio-caudal direction of 1 mm in the exhalation phase with deviations equal or less than 4.5 mm in 99% of cases, thus validating the 5 mm margin used in their technical protocol.[11]

Fundowicz et al. described the technical SBRT protocol for liver metastasis used in their institution emphasizing and

recommending the discussion of all patients in a multidisciplinary tumor board.[12]

Radiobiology is the science that studies the actions of ionizing radiation on living matter. Knowledge of basic concepts of radiobiology is essential to know the action of ionizing radiation on tumors and healthy tissues and to understand what we are doing with our patients. Although from a biological point of view, the major feature that differentiates SBRT from conventional radiation treatment is the delivery of large doses in one or a few fractions which results in a high biological effective dose, the radiobiology of SBRT is poorly understood. Macià reviewed in a simple and understandable way the classical principles of fractionation on tumors, tissues and organs treated with high doses of radiation. He also briefly introduced new and exciting radiobiological concepts such as radiation-induced vascular damage in tumors and radiation-induced immunological effects including the abscopal phenomenon.[13]

Rives et al. reviewed the published data on the dose-local control relationship for primary and secondary liver tumors. They also detailed the toxicity reported and dose constraints for organs at risk proposed in the literature.[14]

The following papers detail single center experience in Liver SBRT implemented with different techniques and dose fractionation.

Garcia et al. showed their experience on treating liver metastasis by cyberknife delivering 3 fractions of 9–20 Gy. Since this technique allows to follow the target intrafraction motion, they outline the high accuracy obtained leading to a low toxicity and a high local control. They compare the obtained results with other local techniques, such as radiofrequency thermal ablation, showing at least comparable results. They also outline the need of evaluation of SBRT with a longer follow-up and in prospective trials to define the role of SBRT as primary treatment for liver MTS in selected patients.[15]

As the cyberkinfe system gives the possibility of tracking the lesion during the beam delivery, the question of dose escalation without increasing toxicity has been investigated by Alejandra Mendez-Romero et al. Forty patients with 55 liver MTS received 3 fractions of 12.5 Gy to 16.75 Gy. Even if the difference in local control was not significant between the two groups, a better local control was observed in the highest dose group without enhancement of toxicity. Even if in the literature dose escalation has been related to an improvement in local control, maybe one explanation for the absence of difference in this study could be the number and the size of lesions included in this study compared to other series in the literature.[16]

Besides the cyberknife system, linear accelerators permit today the possibility of tracking the tumor during the beam delivery thanks to a respiratory gating technique with an external surrogate placed on the patient's abdominal wall associated with implanted fiducial markers in or closed to the tumor to manage liver motion. Two studies have published their experience with this technique. The first one, Rubio et al. evaluated 21 patients with liver metastases receiving 3 fractions of 12–20 Gy or 5 fractions of 10 Gy. The 1- and 2-year local control was 94.4% and 80.6%, respectively, without toxicity above grade 3. They could not establish a correlation between tumoral size or delivered dose and local control.[17]

The second one by Llacer-Moscardo et al. discusses the technique of real-time adaptative gating applied to liver SBRT and the concerns about the accuracy of this technique compared to others. On the other hand, they evaluated their preliminary clinical results which, encouraging as they are, have to be confirmed as follow-up is low. Knowing that tolerance was excellent, they project to carry on with this study focusing on dose escalation.[18]

Amendola et al., evaluated 27 patients with liver metastasis from colon, lung and breast cancer, using image-guided SBRT with abdominal compression. They delivered 3 fractions of 12–20 Gy. They found a better outcome in patients with smaller tumors, treated at higher doses and depending on histologic type, confirming results of previous published data.[19]

Another clinical situation is the treatment of breast cancer liver metastasis by SBRT. Those tumors, when well selected, present a better prognosis than other types of liver metastasis with 2-year overall survival ranging from 30 to 76%. (REF) Scorsetti et al. have published here their series about 23 patients with 33 lesions. The actuarial 1- and 2-year local control was excellent (96% and 87%) using 48–60 Gy in 3 fractions. They outline the need of clinical trials to determine which patients will benefit of this technique as a curative intent.[20]

The last article discussed the important question about the evaluation of the response to hepatic SBRT. Tetreau et al. reviewed the scarce literature on this topic, concluding that RECIST criteria are inadequate in the evaluation of the response for hepatic metastases and hepatocellular carcinoma treated by SBRT and that there is much work to be done on this issue that is critical to accurately measure the results.[21]

We hope that this special issue focused on SBRT for liver tumors will be interesting for colleagues dedicated to this field.

We want to dedicate this work to the memory of our colleague, Ludovic Bedos that left us the on the 23th of July. We will always remember his humanity and his excellent professional qualities. He was working as a physicist in the Department of Radiation Oncology at the Cancer Institute of Montpellier (ICM) and was specially implicated in stereotaxic body radiation therapy.

Conflict of interest

None declared.

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REFERENCES

1. Potters L, Steinberg M, Rose C, et al. American Society for Therapeutic Radiology and Oncology and American College of Radiology Practice guideline for the performance of stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2004;**60**(4):1026–32.
2. Martin A, Gaya A. Stereotactic body radiotherapy: a review. *Clin Oncol* 2010;**22**:157–72.

3. Rubio C, Morera R, Hernando O, Leroy T, Lartigau SE. Extracranial stereotactic body radiotherapy. Review of main SBRT features and indications in primary tumors. *Rep Pract Oncol Radiother* 2013;**18**(6):387–96.
4. Tree A, Khoo V, Eeles R, et al. Stereotactic body radiotherapy for oligometastases. *Lancet Oncol* 2013;**14**:e28–37.
5. Mantel F, Flentje M, Guckenberger M. Stereotactic body radiation therapy in the re-irradiation situation – a review. *Radiat Oncol* 2013:7.
6. Wong SL, Mangu PB, Choti MA, et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorrectal cancer. *J Clin Oncol* 2010;**28**(3):493–508.
7. Adam R, Chiche L, Aloia T, et al. Hepatic resection for noncolorectal nonendocrine liver metastases. Analysis of 1452 patients and development of a prognostic model. *Ann Surg* 2006;**244**(4):524–35.
8. Rabinel P, Dousse D, Muscari F, Suc B. Management of liver cancer. The Surgeon's point of view. *Rep Pract Oncol Radiother* 2017;**22**(2):176–80.
9. Revel-Mouroz P, Otal P, Jaffro M, et al. Other non-surgical treatments for liver cancer. *Rep Pract Oncol Radiother* 2017;**22**(2):181–92.
10. Riou O, Llacer Moscardo C, Fenoglietto P, et al. SBRT planning for liver metastases: A focus on immobilization, motion management and planning imaging techniques. *Rep Pract Oncol Radiother* 2017;**22**(2):103–10.
11. Bedos L, Riou O, Aillères N, et al. Evaluation of reproducibility of tumor repositioning during multiple breathing cycles for liver stereotactic body radiotherapy treatment. *Rep Pract Oncol Radiother* 2017;**22**(2):132–40.
12. Fundowicz M, Adamczyk M, Kołodziej-Dybasí A. Stereotactic body radiation therapy for liver metastasis – the linac-based Greater Poland Cancer Centre practice. *Rep Pract Oncol Radiother* 2017;**22**(2):158–62.
13. Macià M. Radiobiology of stereotactic body radiation therapy (SBRT). *Rep Pract Oncol Radiother* 2017;**22**(2):86–95.
14. Rives M, Izar F, Parent L, et al. Dose to organs at risk and dose prescription in liver SBRT. *Rep Pract Oncol Radiother* 2017;**22**(2):96–102.
15. Garcia R, Santa-Olalla I, Lopez Guerra JL, et al. Robotic radiosurgery for the treatment of liver metastases. *Rep Pract Oncol Radiother* 2017;**22**(2):111–7.
16. Mendez Romero A, Keskin-Cambay F, van Os RM, et al. Institutional experience in the treatment of colorectal liver metastases with stereotactic body radiation therapy. *Rep Pract Oncol Radiother* 2017;**22**(2):126–31.
17. Rubio C, Hernando-Requejo O, Zucca Aparicio D, et al. Image guided SBRT for multiple liver metastases with ExacTrac® Adaptive Gating. *Rep Pract Oncol Radiother* 2017;**22**(2):150–7.
18. Llacer-Moscardo C, Riou O, Azria D, et al. Imaged-guided liver stereotactic body radiotherapy using VMAT and real-time adaptive tumor gating. Concerns about technique and preliminary clinical results. *Rep Pract Oncol Radiother* 2017;**22**(2):141–9.
19. Amendola BE, Amendola MA, Blanco JM, et al. Radiosurgery for liver metastases. A single institution experience. *Rep Pract Oncol Radiother* 2017;**22**(2):118–25.
20. Scorsetti M, Franceschini D, De Rose F, et al. The role of SBRT in oligometastatic patients with liver metastases from breast cancer. *Rep Pract Oncol Radiother* 2017;**22**(2):163–9.
21. Tetreau R, Llacer-Moscardo C, Riou O, et al. Evaluation of response after SBRT for liver tumors. *Rep Pract Oncol Radiother* 2017;**22**(2):170–5.

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