



# Should we incorporate ablative radiotherapy in standard treatment of advanced intrahepatic cholangiocarcinoma?

Giovanni Brandi<sup>1</sup>, Andrea Palloni<sup>1</sup>, Alessio Giuseppe Morganti<sup>2</sup>

<sup>1</sup>Unit of Medical Oncology, <sup>2</sup>Radiation Oncology Center, Department of Experimental, Diagnostic and Specialty Medicine, Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

*Correspondence to:* Giovanni Brandi. Unit of Medical Oncology, Sant'Orsola-Malpighi Hospital, University of Bologna, Via Massarenti 9, 40138 Bologna, Italy. Email: giovanni.brandi@unibo.it.

*Comment on:* Tao R, Krishnan S, Bhosale PR, *et al.* Ablative Radiotherapy Doses Lead to a Substantial Prolongation of Survival in Patients With Inoperable Intrahepatic Cholangiocarcinoma: A Retrospective Dose Response Analysis. *J Clin Oncol* 2016;34:219-26.

Submitted Aug 10, 2016. Accepted for publication Aug 16, 2016.

doi: 10.21037/tcr.2016.08.19

View this article at: <http://dx.doi.org/10.21037/tcr.2016.08.19>

Cholangiocarcinoma still remains a rare neoplasm, but the great and rapid increase in incidence, especially of the intrahepatic form probably caused by exposure to unsuspected but extremely widespread risk factors as asbestos (1), makes it necessary that every oncologist acquires the appropriate knowledge for management of cholangiocarcinoma, a challenging disease in the oncology landscape. As the diagnostic and therapeutic pathway for cholangiocarcinoma can be declined in different modalities, patients should early referred to a multidisciplinary team in tertiary center where all diagnostic and therapeutic tools are available and where there's familiarity with patients management algorithm (2). A recent study by Tao and colleagues (3) suggests that a powerful new weapon can be helpful in the management of intrahepatic cholangiocarcinoma (IHCC). In their study the authors used advanced techniques of radiation therapy (RT) in patients with inoperable IHCC. The purpose of the study was to deliver to these patients ablative doses of radiation. Their technique was based on the use of intensity modulated RT or passive scatter proton beam technique, combined with image guided breath hold methods. The RT technique has been further optimized through the use of simultaneous integrated boost (SIB). The use of the SIB allowed to administer a higher dose to the central region of the tumor and to reduce the dose to surrounding healthy organs. This study is particularly original in terms of used technique. In fact, in patients with larger neoplasm, a boost to the central part of the tumor was delivered, to a volume defined as gross tumor volume—1 cm. The rationale of this

choice was to administer a higher dose to the inner, hypoxic and therefore radioresistant part of the tumor. It might be objected that the internal target as defined by the authors does not necessarily match with the hypoxic fraction. In fact, the identification of the less oxygenated tumor sub-volume would require functional/metabolic imaging methods. We must remember that IHCC is a highly heterogeneous tumor relatively to size (usually large since discovered late) and to causal risk factors. This can impact the response to systemic therapy (chemotherapy/molecular targeted therapy) but also to radiotherapy (4). In the study of Tao and colleagues a very high and truly “ablative” dose was delivered in this way without significant toxicity. This finding justifies further studies of dose escalation to the inner and radioresistant tumor areas, as suggested for example in H&N tumors. A treatment with ablative doses selectively delivered within the tumor may be associated with several advantages. Among these we can hypothesize an improved response/downstaging, a better palliative effect, and an immunoenhancing effect. The results were encouraging. Median survival was 30 months and 3-year survival was 44%. But the most interesting feature was the correlation between biological equivalent dose (BED) and survival. Actually, survival was significantly superior ( $P=0.02$ ) in patients with higher dose (BED  $>80.5$  Gy: median not reached) *vs.* lower dose (BED  $\leq 80.5$ : 27 months). Three-year survivals were 73% and 38%, respectively. Multivariate analysis confirmed the favorable impact of higher doses on local control and survival. Finally, the treatment was relatively well tolerated with no documented cases of

radiation-induced liver disease. Despite encouraging data, the study has several limitations, highlighted by Brade and Dawson (5). Among these limits should be highlighted the retrospective design, the possible underestimation of adverse events, and the lack of homogeneity of doses, fractionation and chemotherapy regimens. Furthermore, some administered doses (60 Gy in 2 Gy/fraction) are far to be considered “ablative”. Finally, information on the results in terms of clinical response and downstaging are lacking. Therefore, this treatment seems to have some potentialities ranging from a downstaging approach with neoadjuvant intent until definitive treatment (such as occurs for prostatic neoplasms). Actually, one of the most interesting discussion topics proposed by the work of Tao *et al.* is the comparison between ablative radiotherapy doses and surgery as definitive treatment of IHCC. To date surgical approach is the best treatment strategy in patients with potentially resectable tumors. However, only about a third of patients at time of diagnosis undergoes surgery with curative intent because of local extent of disease, poor clinical conditions, comorbidity and poor hepatic functional reserve (6,7). According to the most recent data, median survival of patients with IHCC undergoing radical surgery is about 30 months, with 3-year and 5-year OS of 45% and 35%, respectively (7-12). Tao *et al.* obtained, in the subgroup of patients treated with ablative radiotherapy doses, results similar to those of patients receiving surgical treatment. Certainly high radiation doses may increase local tumor control and this study confirms the efficacy in terms of local control of ablative RT in upper GI tumors (13,14). It is also interesting the indirect comparison with chemotherapy alone. In the treatment of advanced disease, chemotherapy has an established role only in frontline setting (15), while the role of a second line and the optimal regimen remains to be determined (16). In addition the experience of our tertiary center shows that there are only sporadic cases (<1%) of durable complete response to chemotherapy alone. However, few studies evaluated efficacy of chemotherapy only in patients with IHCC. In the study by Kostantinidinis *et al.* (17) on patients with locally advanced IHCC receiving systemic +/- intrahepatic chemotherapy, median survival was 24.1 months in patients with intrahepatic IHC alone. Instead, in the study of Tao and colleagues, overall median survival was 30 months. While in the metastatic disease the standard of care is systemic chemotherapy with frontline combination of gemcitabine and platinum derivate (cisplatin, but also oxaliplatin) what is the most appropriate strategy for patients with locally advanced cholangiocarcinoma is

debated as there are different local treatments showing their efficacy in association or not with systemic chemotherapy. To date the positive results of high dose RT have been achieved only in non-randomized studies such as Tao's and colleagues study. For this reason, current guidelines do not include this type of treatment. For example, current NCCN guidelines recommend as a primary option for unresectable IHCC the gemcitabine/cisplatin combination therapy (18). In the same guidelines the RT (secondary option) is still represented by standard fluoropyrimidine-based chemoradiation. The NCCN guidelines, finally, consider the possibility of combining chemotherapy with local therapies. However, these do not yet include ablative RT but only other treatment techniques (RFA, TACE, DEB-TACE, TACE drug-eluting Microspheres, TARE with yttrium-90 microspheres) (18). In our opinion high dose radiotherapy could be another “string to our bow” against locally advanced unresectable IHCC, among other different therapeutic arms as radiofrequency ablation, yttrium-90 radioembolization and transarterial chemoembolization that have shown their efficacy in the local control of inoperable disease. For example radiofrequency ablation appears to be effective in patients with a single small (tumor diameter of 3–5 cm) intrahepatic lesion, resulting in a median survival of 33–38.5 months and a 3-year survival ranging from 43% to 83% (19-22).

An Italian group recently analyzed the largest series of patients with IHCC treated with yttrium-90 radioembolization. Despite the heterogeneity and the low number of cases, the results are encouraging: median overall survival was 17.9 months and response rates were 20%, 60% and 70% according to RECIST 1.1, mRECIST and EASL criteria, respectively (23). In order to choose the best therapeutic strategy, a careful selection of patients with locally advanced disease is a crucial point. Given the retrospective nature of the work by Tao *et al.*, we could not exclude that patients able to receive higher doses of RT had probably characteristics that improve their prognosis more likely than patients treated with lower doses. Another issue is the most appropriate method of combining radiotherapy with systemic chemotherapy in patients with locally advanced IHCC, even if high radiation doses providing the best outcome in the study of Tao *et al.* may be not simultaneously associated to chemotherapy. In this study the majority of patients (89%) received chemotherapy before RT but the type, the number of cycles, and the duration of systemic therapies were not specified. In conclusion it's necessary to more accurately confirm the

effectiveness of ablative RT and it remains to be determined what's the best setting of patients with IHCC where the use of this technique is appropriate. It is not probable that it can replace surgical resection as standard treatment of operable patients. By contrast it could play a role in patients inoperable for anatomical issues or poor performance status and also in patients with postoperative intrahepatic recurrences in which a second resection is rarely possible. Another putative field of application of this technique could be as a downstaging method in primary inoperable lesions. In this view innovative combinations of new drugs with ablative RT should be explored, maybe after a careful analysis of molecular factors predicting the response to chemotherapy (24). Ultimately the results of Tao's studies justify the design of randomized studies on the association of chemotherapy and ablative RT in patients with locally advanced, inoperable IHCC, supporting the use of high dose regimen (67.5 Gy in 15 fractions) in the current NRG-GI001 trial, a randomized phase III study comparing the addition of radiotherapy after 3 cycles of gemcitabine-cisplatin chemotherapy to chemotherapy alone in patients with unresectable, locally advanced IHCC. However, it should be recognized the difficulties in organizing such studies in relatively rare neoplasms such as IHCC (5). Therefore, it's time to even explore the possibility of alternative trial designs, possibly based on the use of large multi-institutional databases (5).

### Acknowledgments

*Funding:* None.

### Footnote

*Provenance and Peer Review:* This article was commissioned and reviewed by the Section Editor Bo Zhai (Department of Hepatobiliary Surgery, The Fourth Hospital of Harbin Medical University, Harbin, China).

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2016.08.19>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

### References

1. Brandi G, Di Girolamo S, Farioli A, et al. Asbestos: a hidden player behind the cholangiocarcinoma increase? Findings from a case-control analysis. *Cancer Causes Control* 2013;24:911-8.
2. Brandi G, Venturi M, Pantaleo MA, et al. Cholangiocarcinoma: Current opinion on clinical practice diagnostic and therapeutic algorithms: A review of the literature and a long-standing experience of a referral center. *Dig Liver Dis* 2016;48:231-41.
3. Tao R, Krishnan S, Bhosale PR, et al. Ablative Radiotherapy Doses Lead to a Substantial Prolongation of Survival in Patients With Inoperable Intrahepatic Cholangiocarcinoma: A Retrospective Dose Response Analysis. *J Clin Oncol* 2016;34:219-26.
4. Brandi G, Farioli A, Astolfi A, et al. Genetic heterogeneity in cholangiocarcinoma: a major challenge for targeted therapies. *Oncotarget* 2015;6:14744-53.
5. Brade AM, Dawson LA. To RCT or Not to RCT: How to Change Practice for Rare Cancers? *J Clin Oncol* 2016;34:203-4.
6. Bridgewater J, Galle PR, Khan SA, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol* 2014;60:1268-89.
7. de Jong MC, Nathan H, Sotiropoulos GC, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. *J Clin Oncol* 2011;29:3140-5.
8. Ercolani G, Vetrone G, Grazi GL, et al. Intrahepatic cholangiocarcinoma: primary liver resection and aggressive multimodal treatment of recurrence significantly prolong survival. *Ann Surg* 2010;252:107-14.
9. Razumilava N, Gores GJ. Cholangiocarcinoma. *Lancet* 2014;383:2168-79.
10. Mavros MN, Economopoulos KP, Alexiou VG, et al. Treatment and Prognosis for Patients With Intrahepatic Cholangiocarcinoma: Systematic Review and Meta-

- analysis. *JAMA Surg* 2014;149:565-74.
11. Farges O, Fuks D, Boleslawski E, et al. Influence of surgical margins on outcome in patients with intrahepatic cholangiocarcinoma: a multicenter study by the AFC-IHCC-2009 study group. *Ann Surg* 2011;254:824-29.
  12. Luo X, Yuan L, Wang Y, et al. Survival outcomes and prognostic factors of surgical therapy for all potentially resectable intrahepatic cholangiocarcinoma: a large single-center cohort study. *J Gastrointest Surg* 2014;18:562-72.
  13. Brunner TB, Nestle U, Grosu AL, et al. SBRT in pancreatic cancer: what is the therapeutic window? *Radiother Oncol* 2015;114:109-16.
  14. Sanuki N, Takeda A, Kunieda E. Role of stereotactic body radiation therapy for hepatocellular carcinoma. *World J Gastroenterol* 2014;20:3100-11.
  15. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010;362:1273-81.
  16. Fornaro L, Cereda S, Aprile G, et al. Multivariate prognostic factors analysis for second-line chemotherapy in advanced biliary tract cancer. *Br J Cancer* 2014;110:2165-9.
  17. Konstantinidis IT, Groot Koerkamp B, Do RK, et al. Unresectable intrahepatic cholangiocarcinoma: Systemic plus hepatic arterial infusion chemotherapy is associated with longer survival in comparison with systemic chemotherapy alone. *Cancer* 2016;122:758-65.
  18. NCCN Guidelines Version 2.2016. Intrahepatic Cholangiocarcinoma. Accessed on 11 July 2016. Available online: [https://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp](https://www.nccn.org/professionals/physician_gls/f_guidelines.asp)
  19. Kamphues C, Seehofer D, Eisele RM, et al. Recurrent intrahepatic cholangiocarcinoma: single-center experience using repeated hepatectomy and radiofrequency ablation. *J Hepatobiliary Pancreat Sci* 2010;17:509-15.
  20. Kim JH, Won HJ, Shin YM, et al. Radiofrequency ablation for the treatment of primary intrahepatic cholangiocarcinoma. *AJR Am J Roentgenol* 2011;196:W205-9.
  21. Kim JH, Won HJ, Shin YM, et al. Radiofrequency ablation for recurrent intrahepatic cholangiocarcinoma after curative resection. *Eur J Radiol* 2011;80:e221-5.
  22. Kim SA, Lee JM, Lee KB, et al. Intrahepatic mass-forming cholangiocarcinomas: enhancement patterns at multiphasic CT, with special emphasis on arterial enhancement pattern--correlation with clinicopathologic findings. *Radiology* 2011;260:148-57.
  23. Mosconi C, Gramenzi A, Ascanio S, et al. Yttrium-90 radioembolization for unresectable/recurrent intrahepatic cholangiocarcinoma: a survival, efficacy and safety study. *Br J Cancer* 2016;115:297-302.
  24. Brandi G, Deserti M, Vasuri F, et al. Membrane Localization of Human Equilibrative Nucleoside Transporter 1 in Tumor Cells May Predict Response to Adjuvant Gemcitabine in Resected Cholangiocarcinoma Patients. *Oncologist* 2016;21:600-7.

**Cite this article as:** Brandi G, Palloni A, Morganti AG. Should we incorporate ablative radiotherapy in standard treatment of advanced intrahepatic cholangiocarcinoma? *Transl Cancer Res* 2016;5(S3):S450-S453. doi: 10.21037/tcr.2016.08.19