Title: Defining minimum treatment parameters of ablative radiotherapy in patients with hepatocellular carcinoma: An expert consensus

Running Title: Parameters defining "ablative" radiotherapy for HCC

Authors:

Ted K. Yanagihara*, M.D., Ph.D.
Joel E. Tepper*, M.D.
Maria Reig*, M.D., Ph.D.
Andrew M. Moon*, M.D.
Aisling Barry*, M.D.
Meritxell Molla*, M.D.
Jinsil Seong*, M.D.
Ferran Torres*, M.D., Ph.D.
Smith Apisarnthanarax, M.D.
Michael Buckstein, M.D.
Higinia Cardenes, M.D., Ph.D.
Daniel T. Chang, M.D.
Mary Feng, M.D.
Chandan Guha, M.D.
Christopher L. Hallemeier, M.D.
Maria A. Hawkins, M.D.
Morten Hoyer, M.D.
Hiromitsu Iwata, M.D.
Salma K. Jabbour, M.D.
Lisa Kachnic, M.D.
Jordan Kharofa, M.D.
Tae Hyun Kim, M.D.
Alexander Kirichenko, M.D., Ph.D.
Eugene J. Koay, M.D.
Hirokazu Makishima, M.D.
Joel Mases, M.D.
Jeffrey J. Meyer, M.D.
Pablo Munoz-Schuffenegger, M.D.
Dawn Owen, M.D., Ph.D.
Hee Chul Park, M.D., Ph.D.
Jordi Saez, M.D.
Nina N. Sanford, M.D.
Marta Scorsetti, M.D.
Grace L. Smith, M.D.
Jennifer Y. Wo, M.D.
Sang Min Yoon, M.D., Ph.D.
Theodore S. Lawrence*, M.D., Ph.D.
Laura A. Dawson*, M.D.

*Steering Committee

Corresponding Author
Ted K. Yanagihara*, M.D., Ph.D.
Department of Radiation Oncology
Lineberger Comprehensive Cancer Center
University of North Carolina
101 Manning Drive
Chapel Hill, N.C. 27514
tky@unc.edu

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Abstract

Background

The Barcelona Clinic Liver Cancer (BCLC) system does not comment on the use of external beam radiotherapy (EBRT) in hepatocellular carcinoma (HCC) due to a lack of sufficient evidence and intends to perform an individual patient level meta-analysis of ablative EBRT in this population. However, there are many types of EBRT described in the literature with no formal definition of what constitutes "ablative." Thus, we convened a group of international experts to provide consensus on the parameters that define ablative EBRT in HCC.

Methods

Parameters related to dose, fractionation, radiobiology, target identification, and delivery technique were identified by a Steering Committee to generate seven Key Criteria (KC) that would define ablative EBRT for HCC. Using a modified Delphi (mDelphi) method, experts in the use of EBRT in the treatment of HCC were surveyed. Agreement in ≥ 70% of respondents was considered consensus for each KC.

Results

Of 40 invitations extended, 35 (88%) returned responses. In the first round, three of seven KC reached consensus. In the second round, 100% returned responses and consensus was reached in three of the remaining four KC. The distribution of answers for one KC, which queried the α/β ratio of HCC, was such that consensus was not achievable. Based on this analysis, ablative EBRT for HCC was defined as a BED10 ≥ 80 Gy with daily imaging and multi-phasic contrast used for target delineation. Treatment breaks (e.g., for adaptive EBRT) are allowed, but the total

treatment time should be ≤ 6 weeks. Equivalent dose when treating with protons should use a conversion factor of 1.1 but there is no single conversion factor for carbon ions.

Conclusion

Using a mDelphi method assessing expert opinion, we provide the first consensus definition of ablative EBRT for HCC. Empiric data are required to define the α/β of HCC.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer death worldwide [1]. There are many locoregional treatments available, including external beam radiation therapy (EBRT), [2] and consensus guidelines help establish standards of care, including defining contexts when one local therapy is prioritized over another. The Barcelona Clinic Liver Cancer (BCLC) staging system is the most used staging system around the world for selecting a patient's first treatment option and is endorsed by the European Association for the Study of the Liver (EASL) [3] and American Association for the Study of Liver Diseases (AASLD) [4]. In the most recent update, the BCLC treatment algorithm does not provide recommendations regarding the use of EBRT, citing a lack of sufficient prospective data. [5]

To better understand the role of EBRT in the management of HCC, the BCLC and experts in the field have initiated an international effort to perform a systematic literature review and obtain individual patient-level data from qualifying studies for meta-analysis. For this type of review, consensus is needed to define the parameters that constitute ablative EBRT, where the goal of treatment is complete tumor eradication in the targeted area.

Several challenges were identified leading up to the systematic literature review regarding how best to account for treatment intent, technique, and quality of EBRT delivered in defining ablative radiation therapy. For example, the intent of treatment may be curative or EBRT can be used as a bridge to transplant; modalities can include photons, protons, or heavy ions; and a variety of dose-fractionation schemes with varying dosimetric goals, target delineation and motion management can be employed. To obtain meaningful information on the value of EBRT in the BCLC individual-data meta-analysis, a definition of the minimum

technical requirements for radiation treatment parameters used in the curative setting for HCC is needed.

To develop a consensus definition of ablative EBRT, we followed practices used to generate EASL Clinical Practice Guidelines [3]. Specifically, we convened two international committees with expertise in the management of HCC and used a modified Delphi (mDelphi) method to establish consensus on a set of minimum parameters required for EBRT to be considered ablative. This information is essential for the BCLC individual-data meta-analysis, but also can be used generally in considering EBRT treatment approaches for HCC.

Methods

Steering Committee

A committee that included seven radiation oncologists with expertise in the treatment of HCC conferenced to create a list of Key Criteria (KC) by which ablative radiation would be defined. The committee was instructed to identify the *technical parameters* of ablative radiation rather than selecting the correct *patient population* for treatment.

The Steering Committee consisted of ten individuals: seven radiation oncologists (AB, LD, TL, MM, JS, JT, and TY), two hepatologists who specialize in HCC (AM, MR), and one biostatistician (FT). Preliminary KC (drafted by TY, AM, and JT), which represented common areas of variability between studies identified in the systematic literature review, were provided to the Steering Committee. The committee considered the preliminary KC individually, then met virtually to discuss the value of each KC in defining curative-intent radiotherapy, modify phrasing, generate answer choices, and consider additional parameters that were not

encompassed by the draft KC. Consensus on the content and phrasing of each KC and the answer choices was defined as 80% agreement.

Modified Delphi Committee

Invitations to join the mDelphi Committee tasked with selecting answers to each KC were sent to an international cohort of 40 radiation oncologists with expertise in the treatment of HCC. Candidates for the mDelphi Committee were provided by each member of the Steering Committee. Additional candidates were selected based on their extensive publication record as identified by AM and TY during the systematic literature review. All candidates who were nominated were contacted with an invitation to join (i.e., there was no consultation between members of the Steering Committee regarding who should or should not be invited). Candidates were not informed as to who else was invited or who had joined the mDelphi Committee and results of the analysis were not shared until the final drafting of this manuscript. Radiation oncologists on the Steering Committee also participated in the full mDelphi Committee.

In the first round, invitations were sent via email with a document explaining the rationale for the BCLC meta-analysis and goals of defining the technical parameters of ablative radiotherapy. In addition to the seven KC, invitees were also provided a table with examples of dose and fractionation regimens commonly used in the literature along with the biological effective dose (BED) corresponding to a range of α/β ratios **(Table 1)** – explanations for BED and α/β are provided in the Discussion section. Further, one of the KC referred to the use of altered fractionation regimens in HCC and to give context to the meaning of this phrase, a publication [6] was included with the invitation as an example of altered fractionation. All KC had a "comments" section for respondents to provide free text input. Agreement in 70% of respondents was used as the definition of consensus.

Individuals who accepted the invitation were given 30 calendar days to provide their answers and comments for all seven KC. Responses were tabulated and all KC that did not have at least 70% agreement on a single answer were rephrased for a second round. Rephrasing was performed where participants were asked if they "agree," "disagree," or were "neutral" with respect to the most commonly selected answer choice for each KC. A second round of surveys were distributed to all individuals who completed the first round and participants were given 14 calendar days to complete the task. Results were distributed/collated with Qualtrics software (Qualtrics, Provo, UT).

Results

Defining Key Criteria for the mDelphi survey

Each member of the Steering Committee independently reviewed eight concepts for KC to consider how each of the following might be used to generate a definition for ablative radiotherapy: 1) the α/β ratio of HCC, 2) how BED affects tumor control 3) what radiobiologic equivalent (RBE) to use for protons, 4) what RBE to use for carbon ion, 5) the maximum total treatment duration of radiotherapy, 6) use of daily image guidance, 7) use of multi-phase imaging for target contours, 8) number of treatment fractions. After independent review of draft KC, members of the Steering Committee met to discuss each and then voted anonymously on the final phrasing and answer choices. After a second round of drafting and independent voting, seven KC were accepted **(Table 2)**.

Modified Delphi Committee Responses

One of the invitees declined and two of the invitees nominated a different member at their institution to join the committee as their replacement, including one who had already been invited. Therefore, 39 invitations (98%) accepted the invitation to participate in round one of the mDelphi process. Of these, 35 surveys (90%) were returned within the allotted time.

After the first round, consensus was reached in three of seven questions **(Table 3 and Supplemental Figures 1 – 7)**. Answers were provided for all KC by all respondents except for KC4, which queried the RBE of carbon ion radiotherapy. For KC4, multiple respondents commented that it was challenging to select one answer due to the inherent variation in the carbon RBE throughout the range of carbon in tissue, and three participants abstained.

The four KC where there was no consensus in the first round (KC1, KC2, KC4, and KC5) were discussed in the Steering Committee and rephrased **(Table 4)** and resubmitted via web survey to the participants. All 35 (100%) respondents who participated in round 1 completed the second round of the mDelphi process. One respondent abstained from answering KC4 but did answer all other questions and this missing data did not affect the results (i.e., consensus was met without this response). Consensus was met (≥ 70% agreement) for three of the four remaining KC **(Table 5 and Supplemental Figures 8 – 11)**. KC1, which queried the α/β ratio of HCC, did not reach the threshold for consensus because 24 of 35 (69%) respondents felt that a value of 10 could be used, whereas 6 of 35 (17%) were neutral and 5 of 35 (14%) disagreed. Many comments were submitted by respondents regarding uncertainties in the α/β ratio of HCC with some pointing to evidence suggesting that the value was anywhere from 1 to > 10. Therefore, consensus was met for six of the seven KC **(Table 6)**, but without more conclusive empiric evidence, it was thought that expert consensus could not be relied upon to define the single working α/β ratio for HCC.

Discussion

EBRT is not part of the 2022 BCLC guidelines for the management of HCC, which provide treatment recommendations to the international community [5]. With members of the BCLC, we are seeking to synthesize existing data to inform these guidelines through a meta-analysis of individual patient data. The outcomes from this analysis will be heavily dependent on a clear definition of what parameters constitute ablative EBRT. In addition, AASLD guidelines [4] endorse EBRT as an alternative to ablative therapies for BCLC-A HCC, but do not define ablative EBRT or otherwise provide information on appropriate EBRT practices (e.g., dose and technique). Thus, these results could be used in updating future versions of AASLD guidelines.

To date, there is no widely accepted definition for "ablative" EBRT in the management of HCC. Ablative EBRT is often equated with stereotactic body radiotherapy (SBRT), sometimes referred to as stereotactic ablative radiotherapy (SABR), but the term "ablative" implies a biological effect that can provide complete tumor eradication, whereas SBRT and SABR refer to a treatment technique. Further, SBRT and SABR have variable definitions globally. In the United States, the definition is arbitrarily limited by insurance payors according to the number of treatments (i.e., five fractions may be considered SBRT, but six fractions may not). Also, SBRT is often used only in reference to photon-based treatment, but not proton or carbon ion. In this study, there were challenges in reaching consensus regarding the biological parameters that guide ablative radiotherapy, whereas the technical aspects of treatment were more-easily agreed upon:

KC Assessing Biological Aspects of Ablative EBRT (KC1-4)

The question with the most heterogeneity in responses was regarding the α/β ratio of HCC and consensus could not be reached using this mDelphi approach. A full explanation of α/β is beyond the scope of this report. Briefly, several mathematical models have been proposed to estimate the probability that a dose of radiation will kill a cell. These models must account for variability in how cells of different tissues (e.g., bone, lung, liver) are affected by a given dose of radiation. The most commonly used model, the linear-quadratic model, accounts for this heterogeneity with two variables: α and β. Measuring cell kill on a log-normal plot (where exponential decay appears linear), the linear-quadratic model computes the surviving fraction (SF) of cells following a dose of radiation (d) after a number of fractions (N) with the equation: $SF = \exp [-N (\alpha \times d + \beta \times d^2)]$. Here, α accounts for the proportion of cells that are killed as a linear function of radiation dose (on a log-normal plot) while β accounts for the proportion of cells that are killed as a function of the square of the dose (a quadratic relationship). An understanding of α and β for a given type of cancer (e.g., HCC) and the differential values for the surrounding normal tissues (e.g., healthy liver) is important because this difference underlies some of the rationale for selecting the dose and fractionation. The ratio of α/β is derived through experimentation and, although this equation was developed to describe the effects of radiation on cells in culture, this formalism has been useful in describing tumor control as well. For a full description of the linear-quadratic model please see Hall and Giaccia [7].

Human tumors have α/β ratios that vary widely [8]. Commonly, solid tumors with rapid growth have a high α/β ratio of around 10 (e.g., head and neck squamous cell carcinomas [9,10]), but many slowly growing tumors have much lower α/β ratios, as low as < 3 (e.g., prostate [11,12] and breast [13,14] adenocarcinoma), which approximates that of many normal tissues. In the literature, and clinical practice, many investigators simply assign a high α/β ratio, most

commonly 10, to all tumors, partially because a bulk of data exist for rapidly growing head and neck cancers. The literature estimating α/β for HCC is sparse and experiments using cell culture lines have revealed a range of potential values [15] and *in vivo* human data are very limited [16,17] **(Supplemental Table 1)**.

Given the great uncertainty in the actual value of the α/β ratio for HCC, we intend to use a range of values from 2 – 10 in the BCLC meta-analysis. Because individual patient-level data, including prescription dose and rate of tumor control, will be analyzed, this may allow for a better determination of the actual α/β ratio for HCC.

One cannot evaluate outcomes of ablative-intent radiotherapy in HCC without defining the minimum dose to be considered ablative. However, the concept of "dose" may be used to describe the physical dose (a measure of how much energy is deposited in tissue) or the biological dose (how effective a given amount of energy is in killing cells), and how one defines "ablation" may be subjective. The biological effect of radiation dose depends on the total dose delivered, the dose per fraction and the type of radiation (photons, protons or carbon ions).

We chose to define "dose" as BED [18] **(Table 1)** since this is the best means available of comparing biological dose between variable dose/fractionation schemes, which permits an approximation of equivalent biological effects of radiation across studies. We chose not to require dosimetric parameters in this definition (e.g., minimum planning target volume coverage, minimum or average target dose) due to variability in how dose is prescribed and evaluated in a radiation plan. We expect that the variability in dosimetric parameters across studies will not have a major effect on outcomes but is worthy of further investigation. We advocate for future publications to report doses to target volumes as per the International Commission on Radiation

Units and Measurements (ICRU) report #83 [19], including a spectrum of dose metrics, rather than the intended prescription dose.

BED is a mathematical construct that gives an approximation of the biological effectiveness of a given radiation dose. BED is dependent on α/β, the total physical radiation dose, and the dose per fraction based on the following equation: BED = Total Dose x [1 + Fraction Dose/(α/β)]. Higher BED values are associated with improved tumor control. A BED of ≥ 100 Gy has been used as a threshold to define tumor ablation in other cancer histologies. However, clinical data suggest that HCC may be more radiosensitive than many other tumor types, and several mDelphi respondents commented that their practice has evolved over time toward using lower doses of radiation without an apparent compromise in local control, at a time point ranging from 1 to 5 years.

There were many comments expressing the difficulty in selecting "the minimum ablative dose". It is worth noting that there is a continuous relationship between BED and local control without a clear threshold dose **(Figure 1)**. In the first round of the mDelphi, the majority (26/35, 74%) of participants agreed that the minimum BED for EBRT to be considered ablative should be either 60 Gy (e.g., ~35 Gy in 5 fractions) or 80 Gy (e.g., ~43 Gy in 5 fractions). Of these, the majority (17/26, 65%) selected 80 Gy and in the second round of the mDelphi, 26/35 participants (74%) agreed that 80 Gy was the appropriate minimum BED to be considered ablative.

However, given the prior discussion of α/β ratios, and the heavy dependence of BED on the α/β ratio, our meta-analysis will incorporate BEDs calculated with a range of α/β ratios. This may provide valuable information for future studies. Whereas the mDelphi method did not yield consensus on the α/β for HCC, it did find consensus for the BED to be considered ablative. This is because participants were specifically asked to estimate the BED they consider to be

ablative for HCC using their choice of α/β. Therefore, while our meta-analysis will incorporate a range of α/β and BED values to assess outcomes of EBRT, future analyses should provide a more accurate estimate of the α/β for HCC, and a more objective definition of ablative BED.

Different radiotherapeutic particles (e.g., photons and protons) vary in their radiobiologic efficacy such that a given physical dose (e.g., 50 Gy) will have different biologic effects based on the particle delivering the dose. Therefore, to allow comparison across treatment modalities, a formal agreement on the RBE of protons is needed and this was queried by KC3. There was 88% agreement that an RBE value of 1.1 should be used and for individuals who selected a different value, the rationale alluded to inherent uncertainties (e.g., linear energy transfer, tissue oxygenation) in the RBE estimate. We note that 94% of respondents agreed that the RBE for protons that should be used when comparing results across studies was either 1 or 1.1. Based on our pre-determined threshold for agreement, we have accepted an RBE of 1.1 for protons and plan to use this value in our future meta-analysis.

KC4 queried the RBE of carbon ion and this proved controversial in the first round, where consensus was not reached. Several respondents commented that the variability of RBE along the range of heavy ions made it impossible to select a single number, but many recognized that this created additional difficulty in comparing doses used across studies. After discussion with the Steering Committee, KC4 was rephrased to consider whether a single RBE for carbon ion could be chosen for the purposes of performing a literature review and meta-analysis. With this rephrased question, in the second round of the mDelphi, 25/35 (74%) of respondents agreed that it was *not* appropriate to select a single RBE for carbon ion. Because an RBE for carbon ion could not be chosen, the BCLC meta-analysis will examine each manuscript where carbon ion was used individually. The manuscript reviewers will review the methodology for each

publication to determine what biological equivalence model was used to select dose and consider a range of RBE values to determine if the BED delivered was > 80 GyE.

KC Assessing Technical Aspects of Ablative EBRT (KC5-7)

The aim of KC5 was to provide a definition for the total duration of radiotherapy that could be called ablative. This question was posed because some fractionation schedules for HCC are delivered over a more protracted period relative to a traditional once-daily or every-other-day schedule and data are limited as to how a prolonged treatment interval may affect tumor control probability [6,20], although the existing data do not suggest any decrement in tumor control with the longer treatment duration. In the first round of the mDelphi, the majority (26/35, 74%) of respondents agreed that the total duration should be either < 6 weeks or < 8 weeks. In the second round, 71% (25/35) agreed that the cutoff should be < 6 weeks and this met our criteria for consensus. There were several comments from respondents who emphasized the lack of data regarding the optimal treatment interval, with some comments from respondents who selected shorter treatment intervals (i.e., < 2 weeks or < 4 weeks) explaining that this was chosen based on convention rather than empirical evidence.

There was 97% agreement in KC6, with the statement that daily imaging should be used for internal target alignment. The one member of the committee who disagreed, stated that the use of internal markers (e.g., implanted fiducials, liver anatomy seen on daily cross-sectional imaging) was not exactly "target" alignment, but instead was aligning to an adjacent, proxy, target. This is technically accurate. Therefore, we would consider there to be unanimous agreement that daily imaging for target alignment, including an appropriate proxy structure (e.g., fiducials), should be used.

KC7 stated that target contours should rely on multi-phase contrast-enhanced imaging. Two respondents (6%) were not in agreement with this statement and the remainder of the committee. With multi-phase imaging, lesions may best be seen on arterial, portal, or more delayed time points and the phase or phases that are thought to most accurately define tumor extent are used as the primary image set for contouring. It was noted that there are unusual scenarios where non-contrast imaging can provide appropriate anatomical definition of a lesion due to inherent differences in tissue density relative to non-target tissue. While there are unique cases where tumor can be distinguished from background liver, such as in some patients with non-alcoholic steatohepatitis, this does not obviate the need for multi-phasic imaging to ensure adequate target delineation. It is important to note that vascular invasion may be missed without the use of multiphasic imaging, particularly in cases where MRI is not available. For the purposes of this consensus definition, we have maintained the wording of KC7 given the high degree (94%) of agreement with the statement as originally proposed.

Conclusion

We provide the first consensus definition of ablative EBRT in the management of HCC **(Table 6)**: Target delineation should be performed on multi-phasic imaging and daily image guidance should be used to confirm internal target positioning. A BED10 of ≥ 80 Gy should be delivered over a span of ≤ 6 weeks. When using protons, an RBE of 1.1 should be used to calculate an equivalent dose and no single RBE value is appropriate for carbon ion radiotherapy. There were several technical parameters in this definition where consensus was reached with almost unanimous agreement and others that narrowly reached our predetermined threshold for consensus. The most challenging area to define was related to two closely interrelated topics, the

α/β ratio of HCC and the BED threshold to be considered ablative (which is derived using the α/β ratio). Future empiric study will be needed to clarify this aspect of the definition.

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