

Original Research Article

Protocol for an integrated phase II/III randomised controlled trial of transarterial chemotherapy and sorafenib with or without stereotactic body radiation therapy in patients with nonmetastatic unresectable hepatocellular carcinoma

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ABSTRACT

Background: Vast majority of patients with hepatocellular carcinoma (HCC) present with unresectable disease. In the last decade results of randomized trials and subsequent meta-analyses established trans-arterial chemoembolization (TACE) as standard of care in patients with Barcelona clinic liver cancer (BCLC) stage B. However, there is clearly a need to investigate additional therapeutic options that would consolidate the initial response to TACE. A recent meta-analyses concluded that addition of radiation to TACE had 10-35% improvement in two-year overall survival, however as results of meta-analyses were based on small studies, the need for conducting a high quality randomized study was highlighted. The present study is designed to investigate the role of high dose stereotactic radiation as consolidation therapy after TACE in patients with non-metastatic unresectable HCC.

Methods: Patients diagnosed with non-metastatic unresectable HCC with BCLC stage B/A (medically inoperable) and Child-Pugh's score A-B7 will be eligible. The trial will randomize patients into TACE alone arm or TACE followed by stereotactic body radiation therapy (SBRT). The primary aim is to compare in-field progression free survival (PFS) in phase II and overall survival in phase III between the control (TACE) and intervention arm (TACE+SBRT). The secondary aim is to compare cause specific survival, imaging response and quality of life in control and intervention arms.

Results: First analysis of the study has been planned when patient accrued under phase II study have completed 1 year follow up.

Trail Registration: Clinicaltrials.gov, NCT02794337

Keywords: Carcinoma, Hepatocellular, Radiotherapy, Sterotactic body, Transarterial chemoembolization

INTRODUCTION

The incidence of hepatocellular cancer (HCC) is on the rise in South East Asia as a result of chronic viral hepatitis.¹ Lack of structured screening programmes for high risk population, often leads to patients presenting with large tumors at diagnosis leaving only a small proportion of patients eligible for surgical treatment. Barcelona liver cancer classification (BCLC) is used for risk stratification and treatment recommendation in patients with HCC that recommends TACE as the standard treatment for BCLC B.²

Six randomized studies have investigated the efficacy of TACE against trans-arterial embolization (TAE) or best supportive care and use of TACE leads to 1 year overall survival of 43-62%.³⁻⁷ Three metaanalyses have been conducted till date to confirm treatment effects. The first metaanalysis was published in 2003 by the Barcelona group and included 503 patients.⁸ The metaanalysis concluded that the use of TACE was associated with significant survival benefit. In another metaanalysis including 18 trials and 2466 patients chemoembolization was identified to significantly improve 2 year survival (odds ratio 0.54, 95% CI: 0.33-0.89, $p = 0.01$) when compared against nonactive treatment, however was not found to be more effective than TAE.⁹ A recent cochrane metaanalysis that included 645 patients from 9 trials using TAE/TACE could not confirm the therapeutic benefit of TACE.¹⁰ Though the available data is heterogeneous TACE, continues to be standard of care for BCLC intermediate stage (B) patients and select patients with BCLC A who are not deemed suitable for curative resection.

In the last decade there has been increased interest in using drug eluting beads doxorubicin (DEBDOX) based TACE rather than conventional TACE. DEBDOX potentially provides a higher local effect of the antimetabolic drug with lesser systemic side effects. A phase III study (PRECISION V) randomized patients with intermediate stage HCC to receive doxorubicin based conventional TACE (cTACE) or DEBDOX.¹¹ A total of 212 patients with Child A/B were randomized to receive cTACE or DEBDOX. The primary endpoint of study was MRI response at 6 months. DEBDOX arm had higher rate of complete response (27% vs. 22%), partial response (52% vs 44%) and objective response (63% vs 52%). However the hypothesis of superiority was not met ($p = 0.11$). However increased objective response, reduction in serious liver toxicity and doxorubicin side effects was observed in DEBDOX arm. A recent systematic review concluded that DEBDOX had significant advantage ($p < 0.05$) in objective response in the more advanced patients and overall disease control in more advanced patients ($p = 0.026$). It was also associated a statistically significant reduction in doxorubicin based side effects ($p = 0.0001$).¹² A recent analyses of survival of patients with HCC treated with DEBDOX suggest that in carefully selected patients the median survival

approximates 4 years (54.2 months for Barcelona stage A and 47.7 months in BCLC B, however has not been replicated in most of the other published series including recently published SPACE trial.^{13,14}

The efficacy of sorafenib, a multikinase inhibitor, in advanced HCC has been demonstrated in multicentric phase III randomized trials.¹⁵ Heterogeneous results have been reported in Asian and non Asian population and with duration of sorafenib use after TACE.¹⁶ In a matched pair analysis of patients with advanced unresectable HCC the combination of TACE and sorafenib was associated with 10 month improvement in overall survival (27 months vs 17 months; $p = 0.001$).¹⁷ A randomized trial investigating combination of TACE and sorafenib amongst those who did not progress after TACE did not show any benefit for the combination approach.^{14,16} A recent metaanalysis including comparative study that included 899 patients demonstrated improved time to progression but without survival benefit.¹⁸

In the last decade stereotactic body radiation therapy (SBRT) has been used for treating patients with unresectable HCC. The largest experience of radiation therapy in combination with TACE comes from Asian countries due to high incidence of viral hepatitis associated HCC. A comparative study ($n = 165$) reported outcomes of patients with unresectable HCC treated with either TACE alone or in combination with RT. The study used conventional radiation dose of 30-50 Gy (1.8-2 Gy per fraction). The objective response in the combination group was higher than the TACE group (47.4% vs 28.1%, $p < 0.05$).¹⁹ The 3 year overall survival was higher in the combination group (28.6% vs 9.5%). The study identified Child score, tumor extent and use of radiation as independent predictor of survival.²⁰ Other studies have reported 2 year survival of 10% to 55% with combination of TACE and radiation.²¹⁻²⁴ A metaanalysis from China, that included 5 randomized trials (in Chinese language) and 12 prospective studies included 1476 patients concluded that addition of RT to TACE can lead to 10-35% improvement in overall survival and higher odds of survival at 3 and 5 years.²⁵ Though the metaanalysis included 5 randomized trials the methodological quality of trials was considered suboptimal and authors recommended the need for well conducted randomized studies investigating the role of additional RT.

Unlike conventional radiation wherein treatment is delivered in 5 weeks, SBRT involves delivery of ablative doses in 1-6 large fractions to the target volume over 8-10 days. SBRT is associated with higher cell kill than small protracted fractions. A study in HCC patients that treated patients with SBRT using fraction size 25-37 Gy in 3-5 fractions was associated with local control of 75% at 2 years.²⁶ A study of individualized SBRT from Princess Margaret Hospital Tse et al, confirmed safety of high dose SBRT if an individualised prescription is followed.²⁷ Depending on the effective liver volume irradiated (V_{eff})

an individualised dose per fraction was used for treatment. Using individualised dose prescription the dose could range from 30-60 Gy in 6 fractions. This was associated with one year local control of 65%. Another study used TACE with SBRT in patients with unresectable or medically inoperable HCC.²⁸ After a median of 2 cycles of TACE, patients were treated with SBRT to a dose of 53.6 Gy±6.6 Gy in fraction size of 4.8±0.7 Gy. On univariate analysis tumor volume <125 cc, absence of PVTT, use of higher dose per fraction size, child's grade A were identified to be of prognostic significance. The study reported 3 yr survival of 33% with the combination of TACE and RT with overall survival of 40%.²⁴ Similar 1 and 2 year survivals with combination of TACE and SBRT have been reported by other institutions.^{29,30}

The results of combination approaches are encouraging and provide a strong rationale for a randomized comparison between TACE alone or in combination with SBRT. The impact of local intervention is best tested by impact on infield progression survival and finally on overall survival. Therefore we designed an integrated Phase II/III randomized study wherein the phase II randomized part of the study tests impact on infield progression free survival and if indeed a benefit is demonstrated the study will continue accrual towards the phase III design.³¹

Hypothesis

Phase II randomized study

Addition of SBRT will improve in-field progression free survival (PFS) in patients with advanced unresectable hepatocellular cancer.

Phase III randomized study

Addition of SBRT will improve overall survival (OS) in patients with unresectable hepatocellular cancer.

Study objectives

- The primary aim of this trial is to compare the in-field PFS and OS in control and intervention arms.
- The secondary aims is to compare cause specific survival, OS and quality of life (QOL) between the two groups.
- The tertiary aim is to focus on evaluating the response due to treatment using modified response criteria evaluation for solid tumours (mRECIST).

Study design

The present study is designed as an integrated phase II/III randomized study to study the superiority of SBRT to improve in-field PFS and OS. If the phase II randomized study demonstrates statistically significant improvement in in-field PFS, then patients will be accrued in phase III

study for estimation of benefit toward os. The study will follow permuted block stratified randomisation wherein the study population will undergo stratified randomization to receive tace alone or tace with SBRT (strata: child score, viral marker and BCLC stage). All randomisation will be done electronically through epidemiology and clinical trials unit at advanced centre for treatment research and education in cancer (ACTREC), Tata Memorial Centre.

METHODS

Research setting

The study will be conducted at Advanced Centre for Treatment Research and Education in Cancer and Tata Memorial Hospital, Tata Memorial Centre, Mumbai.

Participation and research eligibility

Inclusion criteria

Patients who are more than 18 years of age, diagnosed with unresectable nonmetastatic HCC with Eastern Cooperative Oncology Group performance status 0-1, Barcelona stage B or medically inoperable Barcelona A with Child Pugh score A-B7 will be eligible. No contraindications should exist for TACE and it should be possible to encompass liver lesions within 1-2 hepatic fields without exceeding safe dose limit constraints to normal liver and with optimal predicted liver volume reserve of >700 cc. Molecular banking of liver tissue is optional.

Exclusion criteria

Patients who have metastatic or nodal disease on staging investigations with child C cirrhosis or previous history of liver failure and expected life span <6 months are excluded from study. Patients are also excluded if patient is suffering from active variceal bleeding or other signs of hepatic decompensation and portal venous thrombosis rendering patients unsuitable for TACE. However if patient is suitable for superselective TACE then can be considered for trial inclusion.

Study procedure

Once included in the study, the following will be the study related procedure.

Initial investigations

Patients with unresectable HCC and eligible as per inclusion criteria will be invited to participate in the study. All patients will need to have undergone AFP, liver function test (LFT), viral markers, chest X-ray and bone scan. Triple phase contrast enhanced computed tomography (CECT) scan and multifunctional magnetic resonance imaging (MRI)/multiparametric positron

emission tomography (PET) will be performed prior to initiation of study related procedures. All patients will be required to complete EORTC QLQ-C30 and HCC18 (available in English, Hindi). Furthermore all patients will be evaluated by the medical gastroenterology team for need for antiviral medications. All patients will also undergo assessment of viral load prior to initiation of treatment.

Randomization

After all preinitiation eligibility criteria have been met, patients will be randomized either into control (TACE) or intervention arm (TACE+SBRT arm). Patients will be stratified as per BCLC stage, child status at diagnosis and HbsAg and HCV status.

Irrespective of arm allocation patients will be started on sorafenib or any other systemic agent that is approved as first line medication for advanced unresectable HCC. Sorafenib will be initiated 2 weeks before 1st TACE at a dose considered appropriate by the treating clinician. Though 400 mg bid is the recommended dose a lower dose may be used as per the judgement of treating clinician. Sorafenib will be omitted on the day of TACE and will be reinitiated 3-5 days after the TACE procedure. After completing all TACE cycles patients will continue to be on sorafenib till progression or 12 months whichever is later. During SBRT, patients will stop sorafenib. This decision is based on reports of enhanced liver toxicity with concurrent sorafenib especially while treating large target volumes.³² Sorafenib will be reinitiated 4 weeks after SBRT completion and will continue to be administered till progression or 12 months whichever is earlier. Sorafenib can however be stopped in patients who fail to tolerate sorafenib even after dose modifications.

TACE arm

Patients randomized to TACE arm will undergo 2-4 cycles of TACE. This will involve catheterization of the feeding vessels and injecting 100 mg of doxorubicin. TACE will be repeated after 4-6 weeks and CT/MRI will be repeated prior to each cycle. QOL will be evaluated at baseline and before each cycle of TACE, two months after completing all sessions of TACE (matched time point with completion of SBRT in interventional arm) and three monthly thereafter. Hepatobiliary common terminology criteria for adverse events (CTCAE) will be completed at baseline and after each TACE cycle and subsequently at each follow up.

TACE + SBRT Arm

Patients randomized to TACE+SBRT arm will undergo 2-4 cycles of TACE and will concurrently receive sorafenib as in standard arm. SBRT will be initiated 4-6 weeks after last TACE procedure. SBRT once initiated will continue for 2-2.5 weeks. QOL will be evaluated at

baseline, before each cycle of TACE, 1 month after SBRT and three monthly thereafter. Hepatobiliary CTCAE will be completed at baseline, after each TACE, before SBRT and after completion of SBRT and subsequently at each follow up.

SBRT details

All patients will undergo multiparametric PET/CT and multifunctional MRI prior to SBRT initiation. For SBRT all patients will be immobilized (preferably in a vacuum bag). All patients will undergo four dimensional CT (4DCT) and contrast enhanced free breathing (FB) scan. While SBRT will be planned using internal target volume (ITV) derived through 4 DCT, treatment with other techniques like respiratory gating, active breathing control, deep inspiratory breath hold is also permitted. Organ at risk (OAR) contouring will include Liver- GTV, Liver-CTV (normal liver), esophagus, stomach, kidneys, heart, lungs, bowel and spinal cord. In addition overlying ribs will also be contoured.

The prescription dose for SBRT will be individualized in each patient according to the Veff based prescription model postulated by the Princess Margaret Group.²¹ All dose will be delivered with hypofractionated technique over 6-10 fractions. The present study aims to deliver biologically equivalent dose of 70 Gy or more in 6-10 fractions over 2-3 weeks to the PTV. Treatment will be individualized for each patient depending on normal liver reserve. While finalizing the plan 95% of the target should be covered by 95% of the prescription isodose. Dose to one thirds of the liver will be restricted to less than 27 Gy and median dose will not exceed 18 Gy. Furthermore volume of normal liver receiving 15 Gy will be restricted to less than 700 cc. None of the stomach and bowel structures should receive max dose of 37 Gy (delivered over 6 fractions). The spinal cord max dose will be restricted to less than 34 Gy and dose to 1/3 rd of the right kidney should not exceed 18 Gy.

Both 3 DCRT and IMRT are permissible for SBRT. The choice of beam energy will be the discretion of treating radiation oncologist. The technique yielding most favorable dose profile to the target volume and maximum sparing of normal structures will be used.

Follow up

All patients will be seen on follow up one month after completion of planned treatment (TACE or TACE+SBRT) and every three monthly thereafter. Follow up investigations will include AFP, LFT, Triple phase CECT scan or MRI and chest X-ray. CTCAE specific to hepatobiliary module and QOL module will be filled at each visit. A small proportion of patients are expected to decompensate as a result of treatment. Multidisciplinary liver team will be consulted for management of intervention related decompensation.

Sample size and statistical considerations

The study is planned as an integrated phase II/III study. The integrated phase II/III study design contains two portions. In the first portion of the study evidence of activity is gathered using in-field PFS. If there is sufficient evidence of activity, accrual continues and enough patients are accrued until phase III endpoint of OS can be assessed. All patients from first and second portion of the study are used in the final overall analysis. The calculation of the sample size for this integrated study was done using the National Cancer Institute (NCI) online program.³³

The study assumes a median PFS and OS of 9 and 18 months respectively. For PFS as an endpoint for phase II randomized study the addition of SBRT would reduce the hazard of in-field progression to 0.5 (PFS at 1 years =25%-50%). Assuming alpha of 0.10 (two sided) and beta of 0.80 a total of 96 patients will be required for phase II randomized study. Accounting for 10% attrition 104 patients will be accrued in phase II study. Stage I analysis will be done when all stage 1 patients complete follow up of 1 year.

If the intervention arm does not demonstrate superiority in PFS at stage I analysis than the study will stop recruiting at 104 patients. If the intervention arm is found to be superior ($p \leq 0.10$) in terms of in-field PFS the study will continue to accrue patients towards phase III design for testing difference in OS. The phase III design assumes that the addition of radiation will reduce the hazards of death to 0.77 (by increasing 2 year OS from 45-58%). Another 257 patients will be required to test the superiority hypothesis. Accounting for 10% attrition towards phase III accrual an additional 282 patients will be required. Accounting all patients included in phase II/III design a total of 386 patients will be needed for the conduct of this integrated design.

Study time lines

Phase II of the study will take 5-6 years for accrual. If the study terminates as a phase II randomized study than the total study duration will be 7 years. However if benefit in PFS is demonstrated patients will be accrued for a total of 10 years with another 2 years of follow up. In this case the study will continue for a total of 12-14 years.

Protocol violations

Major violations

- Patient receiving less than 2 cycles of TACE. This excludes patients who receive less number of cycles due to disease progression.
- Not receiving the prescribed dose of SBRT in the intervention arm.
- Inability to receive sorafenib due to toxicity will not comprise major protocol violation.

Minor violation

- Receiving less than 75% of prescribed dose of SBRT.
- Receiving only 2 cycles of TACE due to noncompliance. However if treating oncologist decides that 2 cycles of TACE are optimal then it would not amount to protocol violation.

Data collection

All trial data will be maintained by the principal investigator of the study at ACTREC, Tata Memorial Centre, Mumbai, India.

Event reporting

All events will be captured with CTCAE V.4.0 and all serious adverse events will be notified to institutional review board within seven working days and all deaths within 24 hours of occurrence.

Trial monitoring

The trial will be monitored at a regular interval by the institutional data and safety monitoring board and its report will be submitted to the ethics committee and institutional review board.

Data analysis plan

Primary aim

The study data will be analysed for the primary aim. The overall proportion of patients in standard and intervention arm will be analysed for their in-field PFS and this will be represented using Kaplan-Meier's curves. If the study proceeds to stage III then OS analysis will be compared using Kaplan Meier's curves.

Secondary aim

Cause specific survival and overall survival

Cause Specific survival will be compared in the control and intervention arms and represented using the Kaplan-Meier graphs

QOL analysis

Standard recommendations of EORTC will be used to analyse QOL data of the two study arms.

Functional imaging

Functional imaging will be interpreted by using quantitative and semiquantitative reporting metrics which will be used to discern the predictive

characteristics of the disease that define the therapeutic outcomes.

DISCUSSION

HCC is common in many Asian countries, of about 80% of cases worldwide and less than 20% are candidates for surgery. TACE alone constitutes standard of care for patients who are unresectable or not a candidate for transplantation. Though recommended in standard guidelines TACE alone leads to suboptimal response in large tumours. So, there may be a benefit with the adding another liver directed treatment (like SBRT) to improve therapeutic outcome. A recent meta-analysis involving 25 non-randomized study reports with 2577 patients reported superior median survival for combination of TACE and radiation than TACE alone (22.7 months vs. 13.5 months; $P < 0.001$). It also demonstrated a progressive benefit in 2-, 3-, 4-, and 5-year survival (Odds Ratio (OR), 1.55 [95% CI, 1.31-1.85]; OR, 1.91 [95% CI, 1.55-2.35]; OR, 3.01 [95% CI, 1.38-6.55]; OR, 3.98 [95% CI, 1.86-8.51] respectively).³⁴ Even though this paves a good argument for the use of TACE with radiation there is dearth of level I evidence for combination treatment. The present trial is therefore designed to investigate the incremental benefit of SBRT on PFS and OS in patients with unresectable non-metastatic HCC.

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SC participated in project concept, design, protocol writing, IRB submission, manuscript preparation, funding application and approval. RE participated in design of study protocol, manuscript draft review and approval of final content. KR will participate in acquisition of data, manuscript preparation and final approval. NS participated in protocol review and approval, patient selection, delivery of protocol treatment, image and data analysis and approval of final content. SK participated in protocol review and approval, patient selection, delivery of protocol treatment, image and data analysis and approval of final content. AP participated in protocol review and approval, patient selection, delivery of protocol treatment, image and data analysis and approval of final content. MG participated in design of study protocol, patient selection, manuscript draft review and approval of final content. SP participated in patient selection, manuscript draft review and approval of final content. VO participated in administering study protocol, patient selection, manuscript draft review and approval of content. MR participated in pathology review of protocol patients, protocol design, manuscript draft review and approval of final content. RP participated in conceptual design, manuscript preparation and final approval (Medical Physics Part). SNP participated in conceptual design, manuscript preparation and final approval (Medical Physics Part). SVJ participated in conceptual design, manuscript preparation and final approval (Medical Physics Part). ED participated in conceptual design, manuscript preparation and final approval

(Medical Physics Part). KJ participated in conceptual design, manuscript preparation and final approval (Medical Physics Part). SK participated in conceptual design, manuscript draft and final approval of version (Statistics Part). VR in function imaging acquisition, analysis, protocol and manuscript preparation and final contents. SM participated in protocol design, hepatology management, manuscript review and final approval of contents. PP participated in protocol design, hepatologist management, manuscript review and final approval of contents. SKS participated in design of study protocol, manuscript draft review and approval of final content.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Memorial Centre Ethics Review Committee

REFERENCES

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer. Available at <http://globocan.iarc.fr>. Accessed on 30 May 2016.
2. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. *Hepatology*. 2002;35:519–24.
3. Lin DY, Liaw YF, Lee TY, Lai CM. Hepatic arterial embolization in patients with unresectable hepatocellular carcinoma- a randomized controlled trial. *Gastroenterology*. 1988;94:453–6.
4. Study G. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. *N Engl J Med*. 1995;332:1256–61.
5. Pelletier G, Roche A, Ink O, Anciaux ML, Derhy S, Rougier P, et al. A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. *J Hepatol*. 1990;11:181–4.
6. Bruix J, Llovet JM, Castells A, Montana X, Bru C, Ayuso MC, et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. *Hepatology*. 1998;27:1578–83.
7. Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet*. (London, England). 2002;359:1734–9.
8. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular

- carcinoma: Chemoembolization improves survival. *Hepatology*. 2003;37:429–42.
9. Cammà C, Schepis F, Orlando A, Albanese M, Shahied L, Trevisani F, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. *Radiology*. 2002;224:47–54.
 10. Oliveri RS, Wetterslev J, Gluud C. Transarterial (chemo) embolisation for unresectable hepatocellular carcinoma. *Cochrane database Syst Rev*. 2011;CD004787.
 11. Vogl TJ, Lammer J, Lencioni R, Malagari K, Watkinson A, Pilleul F, et al. Liver, gastrointestinal, and cardiac toxicity in intermediate hepatocellular carcinoma treated with PRECISION TACE with drug-eluting beads: results from the PRECISION V randomized trial. *AJR Am J Roentgenol*. 2011;197:562-70.
 12. Martin R, Geller D, Espot J, Kooby D, Sellars M, Goldstein R, et al. Safety and efficacy of trans arterial chemoembolization with drug-eluting beads in hepatocellular cancer: a systematic review. *Hepatology*. 2012;59(113):255-60.
 13. Burrel M, Reig M, Forner A, Barrufet M, de Lope CR, Tremosini S, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. *J Hepatol*. 2012;56:1330–5.
 14. Lencioni R, Llovet JM, Han G, Tak WY, Yang J, Guglielmi A, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. *J Hepatol*. 2016;64:1090–8.
 15. Rimassa L, Santoro A. Sorafenib therapy in advanced hepatocellular carcinoma: the SHARP trial. *Expert Rev Anticancer Ther*. 2009;9:739–45.
 16. Kudo M, Imanaka K, Chida N, Nakachi K, Tak WY, Takayama T, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. *Eur J Cancer*. 2011;47:2117–27.
 17. Qu X-D, Chen C-S, Wang J-H, Yan ZP, Chen JM, Gong GQ, et al. The efficacy of TACE combined sorafenib in advanced stages hepatocellular carcinoma. *BMC Cancer*. 2012;12:263.
 18. Wang G, Liu Y, Zhou S-F, Qiu P, Xu L, Wen P, et al. Sorafenib combined with transarterial chemoembolization in patients with hepatocellular carcinoma: a meta-analysis and systematic review. *Hepatol Int*. 2016;10: 501–10.
 19. Lawrence TS, Robertson JM, Anscher MS, et al. Hepatic toxicity resulting from cancer treatment. *Int J Radiat Oncol Biol Phys*. 1995;31:1237–48.
 20. Guo W-J, Yu E-X, Liu L-M, Li J, Chen Z, Lin JH, et al. Comparison between chemoembolization combined with radiotherapy and chemoembolization alone for large hepatocellular carcinoma. *World J Gastroenterol*. 2003;9:1697–701.
 21. Hawkins MA, Dawson LA. Radiation therapy for hepatocellular carcinoma: from palliation to cure. *Cancer*. 2006;106:1653–63.
 22. Li B, Yu J, Wang L, Li C, Zhou T, Zhai L, et al. Study of local three-dimensional conformal radiotherapy combined with transcatheter arterial chemoembolization for patients with stage III hepatocellular carcinoma. *Am J Clin Oncol*. 2003;26:92-9.
 23. Liu M-T, Li S-H, Chu T-C, Hsieh CY, Wang AY, Chang TH, et al. Three-dimensional conformal radiation therapy for unresectable hepatocellular carcinoma patients who had failed with or were unsuited for transcatheter arterial chemoembolization. *Jpn J Clin Oncol*. 2004;34:532–9.
 24. Cheng JC, Chuang VP, Cheng SH, Huang AT, Lin YM, Cheng TI, et al. Local radiotherapy with or without transcatheter arterial chemoembolization for patients with unresectable hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2000;47:435–42.
 25. Meng M-B, Cui Y-L, Lu Y, She B, Chen Y, Guan YS, et al. Transcatheter arterial chemoembolization in combination with radiotherapy for unresectable hepatocellular carcinoma: a systematic review and meta-analysis. *Radiother Oncol*. 2009;92:184–94.
 26. Méndez Romero A, Wunderink W, Hussain SM, De Pooter JA, Heijmen BJ, Nowak PC, et al. Stereotactic body radiation therapy for primary and metastatic liver tumors: A single institution PHASE I-II study. *Acta Oncol*. 2006;45:831–7.
 27. Tse RV, Hawkins M, Lockwood G, Kim JJ, Cummings B, Knox J, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol*. 2008;26:657–64.
 28. Liang S-X, Zhu X-D, Lu H-J, Pan CY, Li FX, Huang QF, et al. Hypofractionated three-dimensional conformal radiation therapy for primary liver carcinoma. *Cancer*. 2005;103:2181–8.
 29. Wu D-H, Liu L, Chen L-H. Therapeutic effects and prognostic factors in three-dimensional conformal radiotherapy combined with transcatheter arterial chemoembolization for hepatocellular carcinoma. *World J Gastroenterol*. 2004;10:2184–9.
 30. Choi BO, Choi IB, Jang HS, Kang YN, Jang JS, Bae SH, et al. Stereotactic body radiation therapy with or without transarterial chemoembolization for patients with primary hepatocellular carcinoma: preliminary analysis. *BMC Cancer*. 2008;8:351.
 31. Wang M, Dignam JJ, Zhang QE, DeGroot JF, Mehta MP, Hunsberger S. Integrated phase II/III clinical trials in oncology: a case study. *Clin Trials*. 2012;9:741–7.
 32. Dawson LA, Brade A, Cho C, Kim J, Brierley J, Dinniwell R, et al. Phase I Study of Sorafenib and SBRT for Advanced Hepatocellular Carcinoma. *Int J Radiat Oncol*. 2012;84:10–11.
 33. POWER V3.0 - National Cancer Institute. Available at <http://dceg.cancer.gov/tools/design/power>. Accessed on 7 June 2016.

34. Huo YR, Eslick GD. Transcatheter Arterial Chemoembolization Plus Radiotherapy Compared With Chemoembolization Alone for Hepatocellular Carcinoma: A Systematic Review and Meta-analysis. *JAMA Oncol*. 2015;1:756–65.

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