Radiotherapy and Oncology 114 (2015) 289–295

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

Charged particle therapy versus photon therapy for patients with hepatocellular carcinoma: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 27 August 2014
Received in revised form 3 November 2014
Accepted 20 November 2014
Available online 9 December 2014

Keywords:
Hepatocellular carcinoma
Radiotherapy
Photon
Carbon-ion
Proton
Meta-analysis

ABSTRACT

Purpose: To perform a systematic review and meta-analysis to compare the clinical outcomes and toxicity of hepatocellular carcinoma (HCC) patients treated with charged particle therapy (CPT) with those of individuals receiving photon therapy.

Methods: We identified relevant clinical studies through searching databases. Primary outcomes of interest were overall survival (OS) at 1, 3, 5 years, progression-free survival (PFS), and locoregional control (LC) at longest follow-up.

Results: 73 cohorts from 70 non-comparative observational studies were included. Pooled OS was significantly higher at 1, 3, 5 years for CPT than for conventional radiotherapy (CRT) [relative risk (RR) 1·68, 95% CI 1·22–2·31; $p < 0·001$; RR 3.46, 95% CI: 1.72–3.51, $p < 0.001$; RR 25.9, 95% CI: 1.64–408.5, $p = 0.02$; respectively]. PFS and LC at longest follow-up was also significantly higher for CPT than for CRT ($p = 0·013$ and $p < 0.001$, respectively), while comparable efficacy was found between CPT and SBRT in terms of OS, PFS and LC at longest follow-up. Additionally, high-grade acute and late toxicity associated with CPT was lower than that of CRT and SBRT.

Conclusion: Survival rates for CPT are higher than those for CRT, but similar to SBRT in patients with HCC. Toxicity tends to be lower for CPT compared to photon radiotherapy.

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Hepatocellular carcinoma (HCC), accounting for 80–90% of primary liver cancer, is the fifth most common solid tumor and the third leading cause of cancer-related death worldwide, which leads to a 500,000 deaths per year [1,2]. Currently, several treatment modalities are available for HCC, including surgical interventions (tumor resection and liver transplantation) [3], percutaneous (ethanol injection, radiofrequency thermal ablation) [4,5] and transarterial (embolization, chemoperfusion, or chemoembolization) interventions [6], systemic chemotherapy [7], small molecular multi-kinase inhibitor [8,9], and radiation. Although HCC is currently known as a radiosensitive tumor, the use of radiotherapy is limited because of the poor radiation tolerance of normal liver to local control doses, and complexity of tumor localization.

However, modern advances in treatment design and delivery have renewed enthusiasm for radiation as an effective local–regional treatment modality for HCC. Modern three-dimensional radiotherapy techniques have allowed clinicians to increase dose conformity while escalating dose to the tumor while sparing more normal liver, thus, largely avoiding radiation-induced liver disease (RILD). Several reports have shown that high-dose irradiation to a portion of the liver could be delivered safely with reasonable treatment efficacy [10,11]. More recently, the development of stereotactic body radio-therapy (SBRT), a technique minimizing RT dose to adjacent normal tissues by delivering high doses of RT in a single treatment or in a small number of fractions with high precision, has generated further promise for liver-directed RT [12]. Moreover, the role of charged particle-based RT in the treatment of HCC is also an area of active investigation [13,14]. The unique physical properties of charged particle therapy (protons and carbon ions)—with rapid fall-off of dose beyond the Bragg peak (a sharp deposition of dose at a specific depth in tissue)—and its greater relative biological effectiveness compared with photon therapy might further augment treatment outcomes, not only by reducing the incidence and severity of complications but also by allowing an escalation in radiation dose to improve tumor control and survival, which cannot be achieved with photon therapy. However, to our best knowledge, there is no head-to-head comparison data available for charged particle therapy versus photon therapy in the treatment of HCC. Therefore, we perform a systematic review and meta-analysis of published work to compare treatment outcomes with charged particle therapy and photon therapy for the management of patients with HCC.

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http://dx.doi.org/10.1016/j.radonc.2014.11.033
0167-8140/

Method and materials

Study design

We developed a protocol that defined inclusion criteria, search strategy, outcomes of interest, and analysis plan. The reporting of this systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements [15].

Procedures

To identify studies for inclusion in our systematic review and meta-analysis, we did a broad search of four databases, including Embase, Medline, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews, from the date of inception of every database to August, 2014. The search included the following terms: ('hepatocellular carcinoma' or 'HCC') and ('hepatocellular neoplasm/radiotherapy' [MESH terms] or 'Carcinoma, hepatocellular/radiotherapy' [MESH terms]) and 'survival' (see search strategy Appendix 1). Additional references were searched through manual searches of the reference lists and specialist journals.

To be eligible for inclusion in our systematic review and meta-analysis, study populations (referred to hereafter as cohorts) had to meet all the following criteria: (1) patients with hepatocellular carcinoma; (2) treatment with photon therapy, charged particle therapy, or combined photon therapy and charged particle therapy; (3) reported outcomes of interest (ie, tumor control, survival, and complications); and (4) from an original study (ie, randomized controlled trial, non-randomized clinical trial, observational studies, or case series). We defined charged particle therapy as radiation therapy using beams of protons, carbon ions, helium ions, or other charged particles. Photon therapy included three-dimensional radiation therapy (3DRT), image-guide radiation therapy (IGRT), intensity-modulated radiation therapy (IMRT), or stereotactic body radiation therapy (SBRT) techniques. We classed patients who received both photon therapy and charged particle therapy as a charged particle therapy cohort.

We excluded studies of photon therapy published before 1990 to ensure we included work incorporating modern radiation therapy techniques. We did not limit by time for charged particle therapy studies. We did not restrict our search to language, country, patients' characteristics, or underlying disease status (ie, primary disease, recurrent disease, primary charged particle therapy or photon therapy, or adjuvant charged particle therapy or photon therapy). We excluded case reports with fewer than five patients, reviews, notes, letters, errata, commentaries, and studies published only as abstracts.

Two investigators (W.X.Q. and S.F.) screened the titles and abstracts of potentially relevant studies. We retrieved the full text of relevant studies for further review by the same two reviewers. A third senior investigator resolved any discrepancies between reviewers. If reviewers suspected an overlap of cohorts in a report, they contacted the corresponding author for clarification; we excluded studies with a clear overlap.

The same pair of reviewers extracted study details independently, using a standardized pilot-tested form. A third investigator reviewed all data entries. We extracted the following data: author, study design, study period, patients' characteristics (sex, age, tumor size, Child Push class, and patients with tumor vascular thrombosis), interventions (radiation dose and fractionation schedule), sample size, length of follow-up, and outcomes of interest. We defined outcomes of interest as overall survival, progression-free survival, locoregional control, toxic effects, functional status, and quality of life. We assessed survival outcomes at 1, 3, and 5 years, while we assess progression-free survival and locoregional control at the longest duration of complete follow-up.

To assess quality, since we included non-comparative (uncontrolled) studies in our systematic review and meta-analysis, we used the Newcastle-Ottawa quality assessment scale [16]. This scale is an eight-item instrument that allows for assessment of patient population and selection, study comparability, follow-up and outcome of interest (Appendix 2). We selected items that focused on representativeness of study patients, demonstration that the outcome of interest was not present at the start of the study, adequate assessment of outcome, sufficient length of follow-up to allow outcomes to arise, and adequacy of follow-up.

Statistical analysis

We prespecified the analysis plan in the protocol. We analyzed all patients who started photon therapy or charged particle therapy, regardless of their adherence to treatment. We calculated event rates of outcome (the proportion of patients who developed outcomes of interest) from the included cohorts for both charged particle therapy and photon therapy. We pooled log-transformed event rates with DerSimonian and Laird random-effect models and assessed heterogeneity using the Mantel–Haenszel test [17]. We used the test of interaction proposed by Altman and Bland to compare log-transformed rates of outcomes between charged particle therapy and photon therapy [18]. When the difference between treatments was significant, we calculated the number needed to treat (NNT) from the absolute difference of the pooled estimates between the two groups. A statistical test with a p-value less than 0.05 was considered significant. To account for the potential effect of publication bias, we used the Duval and Tweedie non-parametric trim-and-fill method [19]. To measure overall heterogeneity across the included cohorts, we calculated the I^2 statistic, with I^2 greater than 50% indicating high heterogeneity. We assessed potential publication bias by visual inspection of the symmetry of funnel plots and with the Egger regression asymmetry test. We did all statistical analyses with Stata version 12.1 (StataCorp, College Station, TX, USA) and comprehensive meta-analysis software version 2.0 (Biostat, Englewood, NJ, USA).

Results

636 studies were identified from the database search, of which 166 reports were retrieved for full-text evaluation. 70 non-comparative observational studies met the inclusion criteria and were included in this systematic review (Appendix 3). We did not find randomized controlled trials or controlled studies that compared charged particle therapy with photon therapy directly. Appendix 4 shows the characteristics of the included studies. From the 70 studies, 73 cohorts were identified. 53 cohorts were treated with photon therapy [11,20–70] (3577 patients) whereas 20 received charged particle therapy [71–88] (1627 patients; Table 2). Overall, 5204 patients were included, with a median age of 67 years (range: 55–81) for the charged particle therapy (CPT) cohorts, 62.4 years (range: 53–74) for SBRT cohorts and 59.0 years (range: 51–68) for the conventional radiation therapy (CRT) cohorts. The median radiation dose and follow-up duration was higher in CPT cohorts than SBRT and CRT cohorts, while the median rate of patients with child-pugh A class was higher in CRT cohorts than CPT and SBRT cohorts (Table 1). Additionally, median tumor size, rate of male, rate of patients with ECOG PS 0–1, or median HCC patients with tumor vascular thrombosis did not significantly differ between groups.

Methodological quality of the included studies was fair; most studies provided adequate outcome ascertainment, enrolled a

Table 1
Baseline characteristics of CPT, SBRT and CRT cohorts.

	CPT cohorts	SBRT cohorts	CRT cohorts	*P* value
Cohorts (*n*)	20	30	23	–
Patients (*n*)	1627	1473	2104	–
Median age (years)	67 (55–81)	62.4 (53–74)	59.0 (51–68)	0.002
Median HCC patients with tumor vascular thrombosis (*n*)	19	4.5	33	0.064
Median tumor size (cm)	4.5	4.4	9.0	0.06
Men (%)	72.3	77.4	85.5	0.064
Median Child-Pugh A class (%)	72.5	72.7	86.3	0.007
Median ECOG PS 0–1 (%)	96.7	91.8	92.8	0.71
Median radiation dose (GyE)*	69.3	37	50.9	<0.001
Median follow-up (months)	23	18	18.4	0.064

CPT, charged particle therapy; SBRT, stereotactic body radiation therapy; CRT, conventional radiation therapy; RBE, relative biological effectiveness.
* GyE = RBE × Gy; RBE of proton beam is 1.1; RBE of carbon ion is 3; ECOG PS, Eastern Cooperation Oncology Group performance status.

Table 2
Comparison of primary outcomes for charged particle therapy cohorts and photons therapy cohorts.

Groups	Cohorts (*n*)	Patients (*n*)	Events (95%)	I^2	Relative risk (95%)	*p*	NNT*
1-year OS							
CPT	6	704	0.79 (0.66–0.88)	86.4	1	–	–
CRT	10	1130	0.47 (0.34–0.60)	93.1	1.68 (1.22–2.31)	<0.001	3.1
SBRT	21	1014	0.80 (0.71–0.87)	87.5	0.98 (0.83–1.18)	0.44	–
3-year OS							
CPT	9	844	0.59 (0.51–0.66)	71.0	1	–	–
CRT	6	528	0.24 (0.17–0.33)	76.5	2.46 (1.72–3.51)	<0.001	2.9
SBRT	7	507	0.58 (0.40–0.74)	90.6	1.02 (0.73–1.42)	0.46	–
5-year OS							
CPT	11	1276	0.37 (0.31–0.43)	74.7	1	–	–
CRT	1	45	0	0	25.9 (1.64–408.5)	0.02	3.7
SBRT	4	308	0.31 (0.17–0.48)	85.5	1.19 (0.69–2.06)	0.26	–
PFS#							
CPT	7	284	0.54 (0.31–0.75)	90.4	1	–	–
CRT	6	340	0.29 (0.11–0.59)	94.1	1.86 (1.08–3.22)	0.013	4
SBRT	7	290	0.36 (0.23–0.51)	80.0	1.34 (0.83–2.72)	0.09	-
Loco-regional control#							
CPT	12	1021	0.86 (0.83–0.88)	42.0	1	–	–
CRT	1	30	0.20 (0.09–0.38)	0	4.30 (2.09–8.84)	<0.001	1.5
SBRT	12	750	0.87 (0.83–0.92)	71.8	0.99 (0.93–1.05)	0.35	–

$I^2 \geqslant 50\%$ suggests high heterogeneity across studies. Abbreviation: CPT = charged particle therapy. NNT = number needed to treat; OS, overall survival; PFS, progression-free survival; CRT, conventional radiation therapy; SBRT, stereotactic body radiotherapy with photons.
* Calculated when the difference between CPT and photon therapy was significant.
# At longest duration of complete follow-up.

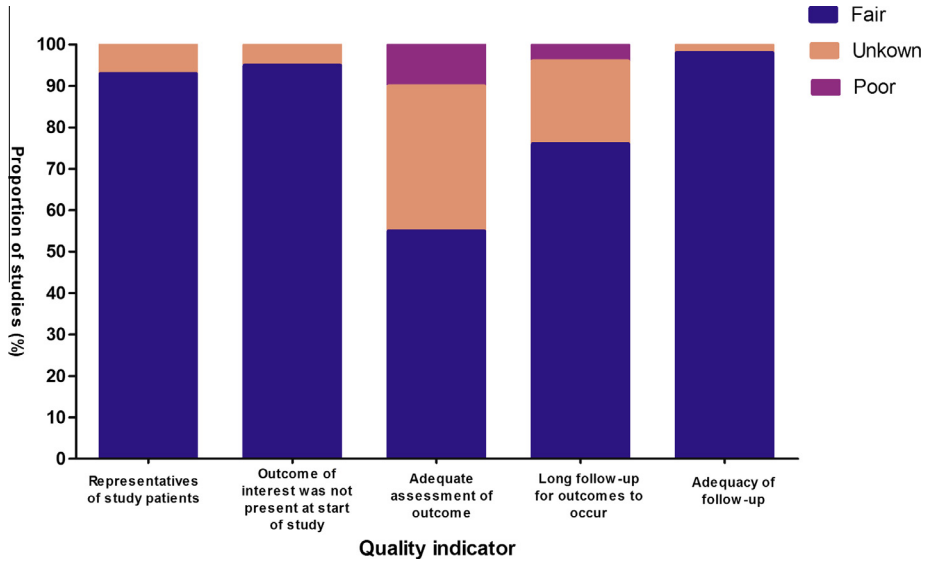

Fig. 1. Selected methodological quality indicator.

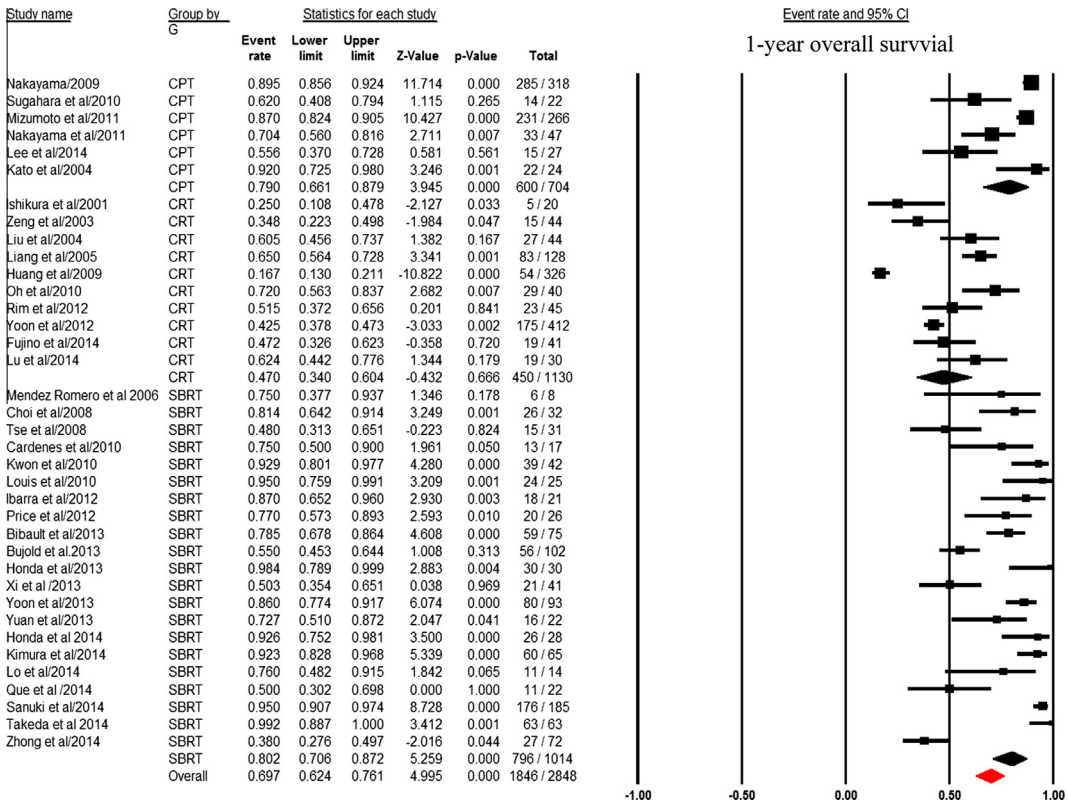

Fig. 2. Forest plot for meta-analysis of 1-year overall survival in patients with HCC.

Table 3
Comparison of ⩾grade 3 acute and late toxic effect event rates for charged particle therapy and photon therapy.

	Included study	Events	Total	Events rate (95%CI)	I^2	p
Acute toxicity						
Hepatic						
CPT	14	21	830	3.1% (1.3–7.6%)	73.8	–
SBRT	19	59	1164	4.9% (3.0–8.1%)	66.8	0.19
CRT	10	111	995	9.9% (6.0–16%)	75.1	0.014
Bone marrow						
CPT	14	40	805	5.1% (1.9–12.7%)	84.3	–
SBRT	11	23	644	4.9% (3.4–7.2%)	0	0.47
CRT	12	26	1015	6.1% (4.3–8.8%)	63.5	0.36
Overall						
CPT	16	68	1172	6.1% (2.8–12.6%)	83.8	–
SBRT	21	137	1221	9.6% (6.0–15.1%)	81.3	0.16
CRT	13	172	1023	20% (13.2–29.2%)	82.8	0.003
Late toxicity						
CPT	7	6	342	2.5% (1.3–4.9%)	0	–
SBRT	6	17	387	6.4% (4.0–10.1%)	50.6	0.011
CRT	5	11	293	6.9% (3.9–1.2%)	75.4	0.011

representative sample of patients, and had an acceptable length of follow-up (Fig. 1). However, comparative evidence was at high risk of bias because we compared data across studies not within them, and selection bias was likely to be present. Assessment of publication bias was not done because data would be unreliable in view of the few studies included for each treatment group and high heterogeneity (I^2 > 50%) in most analyses.

The pooled event rate of overall survival for CPT was significantly higher than that for CRT at 1 year (relative risk 1.68, 95% CI 1.22–2.31; p < 0.001, Table 2 and Fig. 2), at 3 years (relative risk 2.46, 95% CI 1.72–3.51; p < 0.001, Table 2 and Appendix 5), and at 5 years (relative risk 25.9, 95% CI 1.64–408.5; p = 0.02, Table 2 and Appendix 5). Locoregional control was also significantly better at the longest duration of follow-up for patients treated with CPT than for those receiving CRT (4.30, 95% CI: 2.09–8.84; p < 0·001). In addition, the pooled progression-free survival event rate at the longest duration of follow-up was significantly higher for CPT than for CRT (1.86, 95% CI: 1.08–3.22; p = 0.013). However, comparable efficacy was found between CPT and SBRT in terms of OS, PFS and LC at longest follow-up (Table 2), though the 5-year overall survival and progression-free survival event rate at the longest duration of follow-up in CPT seemed higher than that of SBRT (5-year OS: 37% versus 31%; PFS: 54% versus 36%; respectively, Table 2). Further long-term follow-up studies were still needed to investigate this issue.

Table 3 showed the overall (acute and late) occurrence of high-grade (⩾grade 3) toxic effects with charged particle therapy versus photon therapy. There were significantly more acute and late toxicity in the CRT group than in the CPT group (p = 0.003 and p = 0.011, respectively). When stratified by specified acute toxicities, more incidences of acute hepatic toxicity (p = 0.014), but not for bone marrow (p = 0.36), was observed in the CRT group when compared to the CPT group. Additionally, equivalent frequencies of acute toxicities were found between SBRT and CPT groups (p = 0.16). However, there was significantly more late toxicity in the SBRT group than in the CPT group (p = 0.011).

Discussion

To the best of our knowledge, this review and meta-analysis is the first that reviews all evidence and pool the effectiveness and toxicity of CRT, SBRT, carbon-ion and proton radiotherapy in HCC. A total of 70 studies meet the inclusion criteria and are used in the meta-analysis. Based on pooled results, we find that charged particle (proton and carbon-ion) radiotherapy results in a statistically

increased 1-, 3-, 5-year survival, PFS and LC at longest follow-up compared to conventional photon therapy for HCC, while comparable efficacy is found between CPT and SBRT in terms of OS, PFS and LC at longest follow-up. Additionally, our results indicate that CPT is also advantageous in reducing treatment toxicity in HCC when compared to photon therapy. However, more evidence is still required before CPT can become the standard treatment for (subsets of) HCC patients. We could not draw any conclusions about QoL, because it is not reported in any of the included studies.

Prior to our study, a number of literature reviews that separately addressed the effectiveness of CRT [89], SBRT [17,90,91] and particle therapy [13] are recently published. Although no actual meta-analysis of particle therapy in HCC has been published until now, there has been an attempt to calculate pooled estimates for the effectiveness of proton therapy by Dionisi et al. [13]. These estimates are on average lower than the pooled estimates presented in the current study. This difference can be explained by two main factors. First, Dionisi et al. only included proton radiotherapy studies, while carbon-ion radiotherapy comprises an increased radiobiological efficacy to decrease treatment related toxicity and potentially further improve outcome in comparison with proton. Second, the present review includes more recent studies, and especially these newer studies tend to show better results.

The present study has some limitations. Most importantly, the application of formal meta-analytic methods to observational studies has been controversial [92]. One of the most important reasons for this is that the designs and populations of the studies are diverse, and that these differences may influence the pooled estimates. However, when no RCTs are available, as is the case for particle therapy in HCC, a meta-analysis of observational studies is one of the few methods for assessing efficacy and effectiveness [93]. Moreover, it represents the uncertainty surrounding the pooled estimates, and is a valuable method to inform the decision whether more evidence is needed, which is a timely discussion topic with regard to particle therapy [94–96]. However, potential bias may have occurred because the CPT studies are overall older than the SBRT and CRT studies. Another possible source of bias is selection bias. SBRT and especially CPT are highly specialist treatments, only available to a limited number of patients. Finally, the toxicity data are scarcely reported among studies, and as a result it is not possible to adequately compare acute and late treatment toxicity based on clinical data.

Currently available clinical evidence for HCC indicates that survival rates for CPT are significantly higher than those for CRT, but similar to SBRT in patients with HCC. Toxicity tends to be lower for CPT when compared to photon radiotherapy. This suggests that charged particle therapy, with its increased biological efficacy, might be advantageous in the treatment of HCC. However, the overall quantity and quality of data regarding carbon-ion and proton therapy is poor and there might be potential risk of bias in comparisons between observation studies. Thus, the reported results do not allow for definite conclusions. As a result, prospective randomized studies, definitively comparing the survival and treatment toxicity between particle and photon radiotherapy, are strongly encouraged to clearly set the role of CPT in the treatment of HCC.

Funding

None.

Conflicts of interest statement

All authors declare that they have no potential conflicts of interests.

Acknowledgement

We are indebted to the authors of the primary studies, for without their contributions, this work would have been impossible.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2014.11.033.

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