Hepatectomy is still the most cost-effective curative treatment for hepatocellular carcinoma (HCC), but local recurrence remains the dominant pattern of treatment failures, with 5-year recurrence rate as high as 70% [1–3]. In addition, with the improvement of perioperative management, promotion of neoadjuvant treatment, and rise of conversion therapy, an increasing number of patients receiving hepatectomy.

However, there is no clear consensus on the management of adjuvant therapy (AT) for HCC. Radiotherapy (RT) is widely used to treat cancers [7,8], and liver is no longer a contraindication for RT due to the advances in RT techniques and improved understanding of liver tolerance to RT [9]. Novel external beam RT (EBRT) techniques such as three-dimensional conformal RT (3D-CRT), intensity-modulated radiation therapy (IMRT), and stereotactic body RT (SBRT) have helped to achieve satisfactory local control rates (71.4–93.8%) in patients with unresectable HCC [10,11]. On the other hand, adjuvant EBRT has been recommended as the standard treatment for patients receiving radical surgery, but with high risk of recurrence in many types of malignant cancers [12,13]. Internal radiation therapy (IRT) has long been used as a postoperative adjuvant treatment for HCC with promising results, including 131I-lipiodol radioembolization [14], 131I-metuximab for radioimmunotherapy [15], and iodine-125 for brachytherapy [16]. However, there is a paucity of data on adjuvant EBRT.

Yu et al [17] first reported the feasibility of adjuvant 3D-CRT for centrally-located HCC with narrow margin in a single center randomized controlled trial (RCT). However, they found no significant
differences in disease-free survival (DFS) and overall survival (OS) between patients receiving adjuvant 3D-CRT or not. However, in an open-label RCT by Sun et al. [18], adjuvant IMRT was found to significantly improve the recurrence-free survival (RFS) and OS of HCC patients with portal vein tumor thrombus (PVTT) compared with surgery alone. Similarly, Shi et al. [19] identified the anti-recurrence efficacy of adjuvant IMRT following marginal resection for HCC patients with microvascular invasion (MVI) in a superiority RCT. Nonetheless, adjuvant EBRT is not commonly used in clinical settings owing to the uncertain efficacy and concerns pertaining to toxicity [20–23]. Hence, we conducted a systematic review and meta-analysis to synthesize the evidence of the safety and efficacy of adjuvant EBRT for HCC patients receiving hepatectomy.

Materials and methods

This systematic review was conducted according to the preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), which was also registered at https://www.crd.york.ac.uk/PROSPERO/ (Review registry CRD42022332532).

Literature search

A comprehensive literature search was performed using PubMed, MedLine, Embase, Web of Science, and the Cochrane Library to screen eligible studies published in English language as of May 1st, 2022. All studies evaluating the safety and efficacy of adjuvant EBRT for HCC receiving hepatectomy were eligible regardless of whether they were retrospective or prospective.

Eligibility criteria

Inclusion criteria: (i) patients with a pathological diagnosis of HCC; (ii) patients receiving hepatectomy; (iii) arms must include patients receiving adjuvant EBRT, regardless of the modality; and (iv) endpoints must include at least one of the following: DFS, OS, and adverse events (AEs).

Exclusion criteria: (i) population included cholangiocarcinoma or metastatic liver cancer; (ii) patients receiving other adjuvant treatment modality; (iii) duplicate report derived from the same RCT; (iv) data unavailable; and (v) reviews, comments, case reports, or case-series reports.

Definition of endpoints

DFS was defined as the time from resection to recurrence or last follow-up, while OS was the time from resection to death or last follow-up.

Severe AEs were defined as AEs grade ≥ 3 according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Data extraction

According to the predefined protocols, information of each study, including the surname of the first author, year of publication, study period, and baseline characteristics in each arm (sample size, age, sex, population characteristics, and radiation schedule) were independently extracted by two researchers (Lei Wang and Lu Qiú). The hazard ratios (HRs) for DFS or OS were extracted from multivariate analysis or calculated from the Kaplan-Meier curves using Engauge Digitizer 4.1 software [24,25]. In case of any disagreement, the final decision was reached with participation of a third investigator, Qiao Ke.

Quality assessment

The quality of non-randomized studies was determined according to the modified Newcastle-Ottawa Scale (NOS) [26]. Briefly, a study with 0–3 stars was considered to be of low quality, 3–6 stars was considered indicative of medium quality, and ≥7 stars was considered indicative of high quality. The quality of RCTs was determined based on the Cochrane Handbook [27], and a trial with a total score of 0–2 was regarded as low-quality, whereas >2 was considered indicative of high-quality.

Statistical analysis

The primary endpoints in this meta-analysis were DFS and OS, which were determined by HR with 95% confidence interval (CI); the secondary endpoint was AEs, which were determined using odds ratio (OR) with 95% CI. Heterogeneity among the included studies was assessed using χ2 test and I² statistic; P < 0.10 and P < 50% was considered indicative of no significant heterogeneity. In case of significant heterogeneity (P < 0.10 and I² > 50%), the random-effect model was used to estimate the effect size; if not, the fixed-effect model was used [28]. Sensitivity analysis was carried out to verify the stability of the results. Publication bias was determined using Begg’s and Egger’s tests, and the “trim and fill” method was conducted in case there was apparent publication bias. All statistical analyses in this meta-analysis were performed using RevMan Version 5.3 and Stata 14, and two-tailed P values < 0.05 were considered indicative of statistical significance.

Results

A total of 968 records were identified using electronic database. Of these, 73 records were excluded because of duplication, and 895 were excluded after screening of titles and abstracts. Then, 33 were excluded due to the following reasons: 26 because of adjuvant international radiotherapy, one because the updated data was available in a latter publication, two because of use of concomitant internal radiotherapy, one for non-clinical study, and three were excluded because these were review articles or comments. Finally, 10 studies were found eligible for this systematic review [18–23,29–32], including one Abstract published in collection of the Asian Pacific Association for the Study of the Liver in 2022 (Fig. 1) [32].

Among the included studies, one was single arm phase II study [20], and the remaining nine were comparative studies including six comparing adjuvant EBRT versus surgery alone [18,19,23,29,30,32], one comparing adjuvant EBRT versus TACE [31], and two comparing adjuvant EBRT, TACE versus surgery alone [21,22], respectively. The study object was HCC with narrow margin, HCC with MVI, and HCC with PVTT. The baseline characteristics of the included studies are summarized in Table 1. Notably, all the included studies were conducted in China and almost all of them were single-center studies. Among all, eight were assessed as high-quality ones [18–20,22,23,29–31] and two were medium-quality ones [21,32].

DFS was evaluated in all the included studies, as well as OS [18–23,29–32]. The median DFS and OS were reported in six comparative studies [18,21,22,29,31,32], including one study on narrow margin [32], three studies on MVI [22,29,31], and two studies on PVTT [18,21]. Significant difference in terms of DFS between adjuvant EBRT and surgery alone was reported in all the included six studies, regardless of presence of narrow margin, MVI, or PVTT (P < 0.05 for all, Table 1). The clinical results of the studies are exhibited in Table 1. Table 2 presents the regimens and parameters of adjuvant EBRT in each of the included study, including the modality, interval time

Materials and methods

This systematic review was conducted according to the preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), which was also registered at https://www.crd.york.ac.uk/PROSPERO/ (Review registry CRD42022332532).
between RT and surgery, dose/fractions, clinical tumor volume (CTV), planned tumor volume (PTV), and dose limitation of organs at risk (OAR). Of note, SBRT was adopted in one RCT, the majority interval time was 4–6 weeks after surgery, and the biologically effective dose (BED) on CTV ranged from 60 to 72 Gy.

Among all, eight were comparative studies [18,19,21–23,29,30,32], including three RCTs [18,19,30] and one retrospective study involving propensity score matching (PSM) [32]. Owing to lack of significant heterogeneity among the studies ($I^2 = 0$, $P = 0.93$; $I^2 = 0$, $P = 0.52$; respectively), the fixed-effect model was used for meta-analysis; the pooled HR for median DFS and OS were both in favor of adjuvant EBRT to surgery alone (HR = 0.36, 95% CI = 0.28–0.46, $P < 0.001$, Fig. 2A; HR = 0.36, 95% CI = 0.28–0.47, $P < 0.001$, Fig. 2B, respectively). Sensitivity analysis showed no significant change in the results after sequential exclusion of one study at a time from the analysis (Fig. 3A, B). The advantage of adjuvant EBRT over surgery alone was also observed in terms of 1-, 2-, and 3-year DFS ($P < 0.05$ for all, Table 3), but not in terms of 5-year DFS ($P = 0.78$, Table 3). Similar findings were observed in terms of 1-, 2-, 3-, and 5-year OS (Table 3).

Among the included studies, four were on patients with narrow margin [19,23,30,32]. The adjuvant EBRT modality was IMRT in one study [23], 3DCRT in one [30], SBRT in one [19], and unknown in one [32] study. Meta-analysis showed that adjuvant EBRT decreased the risk of recurrence by 63% compared to surgery alone (HR = 0.37, 95% CI = 0.23–0.60, Table 4), as well as decreased the all-cause mortality (HR = 0.32, 95% CI = 0.19–0.55, Table 4). Three studies were on patients with MVI including one study of adjuvant SBRT [19,22,29]. The pooled HR for median DFS and OS in adjuvant EBRT group was 0.28 (95% CI = 0.23–0.70, Table 4) and 0.28 (95%
| Studies      | Year       | Design   | Population                          | Treatment          | Patients | Age (years) | Sex (M/F) | Tumor size (cm) | Tumor number (S/M) | Mean DFS (months) | P-value | DFS Rate (1/2/3/5 years) | Mean OS (months) | P-value | OS Rate (1/2/3/5 years) | Quality |
|-------------|------------|----------|--------------------------------------|--------------------|----------|-------------|-----------|----------------|------------------|------------------|---------|-----------------------------|-----------------|---------|-----------------------------|---------|
| Wang 2015   | 2007–2011  | R        | Narrow-margin Close to major vessels | Adjuvant EBRT      | 33       | 55(27–74)  | 31/2      | 31/2 (10 cm)  | 77/6 (10 cm)    | 31/2             | NA      | 0.038                       | 81.8/72.7/64.2/61.4 | 0.009  | 100/93.9/89.1/71.1         | H       |
| Bai 2016    | 2009–2010  | R        | PVTT (I/II)                          | Adjuvant EBRT      | 10       | 47 ± 16    | 9/1       | 11 ± 6        | 7/3 (≥2/2)      | 14.0 ± 2.4      | 0.004  | 0.078*                      | 28.8/–/–/–       | 0.017  | 93.6/93.6/71.1/54.2        | M       |
| Wang 2017   | 2008–2015  | R        | MVI                                  | Adjuvant EBRT      | 44       | 51.3 ± 11.2| 39/5      | 5.63 ± 2.73   | 42/4             | 25.74 ± 8.12    | 0.003  | 67.7/–/–/–                  | 36.53 ± 5.34    | 0.262  | 93.4/80.6/43.7/–           | H       |
| Wang 2019   | 2008–2016  | R        | MVI                                  | Adjuvant TACE      | 42       | 51.4 ± 10.9| 34/8      | 6.15 ± 3.65   | 38/4             | 7.41             | <0.001 | 0.011*                      | 66.7/52.8/36.2/30.7 | 0.164  | 90.2/80.6/36.2/30.7        | H       |
| Sun 2019    | 2013–2016  | RCT      | PVTT(I/II/III/IV)                     | Adjuvant EBRT      | 26       | 49.6 ± 7.7 | 24/2      | 22/4 (5 cm)   | 25/1             | 9.1 ± 1.6       | 0.001  | 15.3/7.7/7.7                | 36.53 ± 5.34    | 0.005  | 76.9/91.2/11.5/–           | H       |
| Wang 2020   | 2005–2018  | CCT      | MVI                                  | Adjuvant EBRT      | 29       | 55.90 ± 8.05| 24/5     | 4.75 ± 2.15   | 27/2             | 41.77           | 0.006  | 86.2/70.5/63.4/40.1/36.1/36.1 | 38.11 ± 3.88    | 0.004  | 93.8/69.4/58.3/38.5/12.8  | H       |
| Rong 2020   | 2007–2012  | RCT      | Narrow-margin Central HCC            | Adjuvant EBRT      | 58       | 53.1 ± 10.5| 51/7      | 4.7 ± 2.6     | 52/6             | 10.26           | 0.030  | 81.0/70.8/60.3/43.9/71.7/50.8/44.2/35.8 | 25.44 ± 4.05    | 0.026  | 96.6/84.5/79.3/54.7/39.5/35.8 | H       |
| Chen 2021   | 2008–2016  | Phase 2  | Narrow-margin                        | Adjuvant EBRT      | 76       | 53(27–90)  | 67/9      | 4.2(1–15)     | 74/2             | NA               | NA     | 85.5/71.1/68.1/51.6        | NA               | NA     | 100/94.7/88.2/72.2         | H       |
| Shi 2022    | 2015–2016  | RCT      | MVI                                  | Adjuvant EBRT      | 38       | 56.42 ± 10.44| 33/5     | 4.87 ± 2.03   | NA               | NA               | 0.005  | 92.1/71.1/65.8/56.1/76.3/57.9/36.8/26.3 | 72.5 ± 7.72    | 0.053  | 100/97.4/89.5/68.4/53.7    | H       |
| Gou 2022    | 2011–2020  | R        | Narrow-margin                        | Adjuvant EBRT      | 78       | NA         | NA        | NA            | NA               | 0.011  | 47.4/12.8/74/45.1/38.5/14.1 | 52.5 ± 14.0    | 0.028  | 97.4/85.9/67.2/70.5/62.8/24.3 | M       |

Notes: HCC, hepatocellular carcinoma; EBRT, external beam radiotherapy; R, Retrospective; RCT, randomized controlled trial; CCT, controlled clinical trial; PSM, propensity score matching; MVI, microvascular invasion; PVTT, portal vein tumor thrombus; M, male; F, female; S, single; M, multiple; DFS, disease-free survival time; OS, overall survival time; *, the p-value for adjuvant EBRT versus adjuvant TACE; NA, not available; M, medium; H, high.
| Studies         | Type for EBRT | Initial time     | Doses                                                                 | CTV                                                                 | PTV                                                                 | Dose limitation of OAR                                                                 |
|----------------|---------------|------------------|----------------------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Wang 2015 [23]| IMRT          | 4–6 weeks after surgery | 50–60 Gy, and been given in daily dose fractions of 2 Gy, 5 days per week, BED of 64.8–72 Gy | tumour bed (indicated by silver markers) plus a 1.0-cm margin expanding the clinical target volume by 0.5 cm in the anterior–posterior and left–right directions and by 1.0 cm in the cranial–caudal direction | normal liver (total liver volume minus gross tumour volume): mean dose ≤ 23 Gy stomach and duodenum: <54 Gy colon: <55 Gy Cord: <40 Gy Kidney: The volume receiving a dose ≥ 20 Gy (V20) was < 50% |
| Bai 2016 [21]  | 3DCRT        | 4 weeks after surgery | Total radiation dose was around 40 Gy (range 32–48 Gy) A daily fraction of 2.0–3.0 Gy was delivered four times per week | resection margin and portal vein | NA | NA |
| Wang 2017 [22]| IMRT/3DCRT    | 8 weeks after surgery | 54–60 Gy 2 Gy/fraction, 5 fractions, BED of 64.8–72 Gy | tumor cutting bed expands a 1-cm margin | CTV added by 0.5 to 1 cm | NA |
| Wang 2019 [31]| IMRT/3DCRT    | 8 weeks after surgery | 54–60 Gy 2 Gy/fraction, 5 fractions, BED of 64.8–72 Gy | tumor cutting bed expands a 1-cm margin | CTV added by 0.5 to 1 cm | NA |
| Sun 2019 [18] | IMRT          | 4 weeks after surgery | 50 Gy 200 cGy/fraction, 5 days per week, BED of 60 Gy | liver parenchymal transection bed plus a 1-cm margin, plus the main trunk of the right and left portal veins | 0.5 cm margin in the left–right and anterior–posterior directions, and by 1.0 cm in the cranial–caudal direction on the basis of CTV | Normal liver: A mean dose was limited to <23 Gy and no more than 30% of the normal liver was exposed to > 30 Gy. Stomach and duodenum: <54 Gy Colon: <55 Gy Spinal cord: <40 Gy Kidney: V20 of left and right kidney was ≤ 30% |
| Wang 2020 [29]| IMRT          | 4–6 weeks after surgery | 54–60 Gy 2 Gy per fraction for 5 days (fraction) per week, BED of 64.8–72 Gy | the tumor cutting bed, indicated by postoperative CT/MR, with a 1-cm margin in three dimensions | a margin of 1.0 cm was added in cranial-caudal directions and 0.5 cm in other directions to generate the planning target volume (PTV) by expanding CTV | Normal liver: A mean dose was limited to <24 Gy; Stomach and duodenum: <54 Gy Colon: <55 Gy Spinal cord: <40 Gy; Kidney: V20 of left and right kidney was ≤ 30% |
| Rong 2020 [30]| 3DCRT        | 4–6 weeks after surgery | 60 Gy delivered using 2 Gy/fraction, 5 d per week | tumor cutting bed plus a 1-cm margin | expanded by 0.5 to 1 cm | NA |
| Chen 2021 [20]| IMRT          | 4–6 weeks after surgery | 50–60 Gy in 25–30 fractions over 5–6 weeks, BED of 60–72 Gy | tumor bed (indicated by silver markers and changes of postoperative imaging) plus a 1.0-cm margin and a 1.5-cm margin in regions where the tumor adhered to major vascular structures | included a 0.5-cm margin in the anterior–posterior and left–right directions and a 1.0-cm margin in the cranial–caudal direction around the CTV | whole liver, mean dose ≤ 24 Gy; stomach and duodenum, maximum dose ≤ 54 Gy, V50 ≤ 10 mL colon, maximum dose ≤ 55 Gy, V52 ≤ 10 mL; spinal cord planning risk volume, maximum dose ≤ 40 Gy; and left and right kidney, V20 ≤ 30% |
| Shi 2022 [19] | SBRT          | 4 weeks after surgery | A total dose of 35 Gy was delivered in a week, BED of 59.5 Gy | marginal parenchyma with width of 1–3 cm, and the tumour bed was included | margin of 5 mm to the CTV | NA |
| Gou 2022 [32] | NA           | NA               | NA                                                                   | NA                                                                   | NA                                                                   | NA |

Notes: EBRT, external beam radiotherapy; 3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; SBRT, stereotactic body radiotherapy; BED, CTV, clinical target volume; PTV, planning target volume; OAR, organ at risk; NA, not available.
Table 3
Comparing the 1-, 2-, 3-, and 5-year disease-free survival and overall survival rates of adjuvant EBRT versus surgery alone.

| Subgroups | Disease-free survival | Overall survival |
|-----------|-----------------------|------------------|
|           | Studies included      | Patients | Effect model | I² | OR (95%CI) | P   | Studies included | Patients | Effect model | I² | OR (95%CI) | P   |
| 1-year    | 8                      | 733      | Fixed        | 0% | 3.27(2.24–4.80) | <0.001 | 8              | 733      | Fixed        | 0% | 5.56(3.09–10.00) | <0.001 |
| 2-year    | 7                      | 672      | Fixed        | 2% | 2.31(1.64–3.29) | <0.001 | 7              | 672      | Fixed        | 0% | 3.01(2.03–4.45) | <0.001 |
| 3-year    | 7                      | 672      | Fixed        | 0% | 2.14(1.52–3.00) | <0.001 | 7              | 672      | Random      | 51% | 2.24(1.29–3.88) | 0.004 |
| 5-year    | 3                      | 351      | Fixed        | 0% | 0.19(0.61–1.94) | 0.780  | 3              | 351      | Fixed        | 0% | 1.08(0.66–1.76) | 0.770  |

Notes: OR, odds ratio; CI, confidence interval.
CI = 0.17–0.46, Table 4), respectively, compared with surgery alone. Two studies were on patients with PVTT [18,21], and the advantage of adjuvant EBRT was also identified in terms of the median DFS (HR = 0.40, 95% CI = 0.28–0.57, Table 4) and OS (HR = 0.42, 95% CI = 0.30–0.60, Table 4).

Four prospective controlled studies including three RCTs were eligible in this study [18,19,29,30]. The pooled HR for median DFS and OS were both in favor of adjuvant EBRT compared with surgery alone (HR = 0.36, 95% CI = 0.24–0.52, P < 0.001; HR = 0.36, 95% CI = 0.23–0.55, P < 0.001; respectively, Table 4). Moreover, the results did not change greatly in the subgroup of retrospective controlled studies (P < 0.001 for both, Table 4).

Three studies had compared the efficacy of adjuvant EBRT versus TACE [21,22,31]. The median DFS in patients receiving adjuvant EBRT was significantly longer than that in patients receiving surgery alone in the two studies on patients with MVI (P < 0.05 for both, Table 1), but comparable DFS was reported in adjuvant EBRT and TACE arms in the study enrolling patients with PVTT (14.0 ± 2.4 months vs 14.0 ± 3.4 months, Table 1). Nonetheless, there was no significant heterogeneity among these three studies (I^2 = 0, P > 0.05). The pooled HR for median DFS and OS was in favor of adjuvant EBRT compared with TACE (HR = 0.42, 95% CI = 0.28–0.65, P = 0.001, Fig. 4A). Likewise, the advantage of adjuvant EBRT was also observed in terms of OS (HR = 0.55, 95% CI = 0.33–0.93, P = 0.020, Fig. 4B).

Intrahepatic recurrence was reported in five comparative studies [19,22,23,29,30]. Meta-analysis showed that adjuvant EBRT decreased the risk of intrahepatic recurrence by 66% compared to surgery alone (OR = 0.34, 95% CI = 0.23–0.50, P < 0.001, Table 5), as well as extrahepatic recurrence (OR = 0.50, 95% CI = 0.26–0.97, P = 0.04, Table 5). Not as expected, adjuvant EBRT was found to decrease the risk of non-marginal recurrence (OR = 0.50, 95% CI = 0.31–0.79, P = 0.003, Table 5) but not that of marginal recurrence (OR = 0.51, 95% CI = 0.20–1.29, P = 0.15, Table 5). Likewise, the divergence was also observed in terms of single lesion (OR = 1.06, 95% CI = 0.50–2.22, P = 0.88, Table 5) and multiple lesions (OR = 0.41, 95% CI = 0.22–0.75, P = 0.004, Table 5).

AEs were reported in seven included studies [18–21,23,29,30], and none of these were fatal AEs. The proportion of overall AEs was 0.653 (95% CI = 0.405–0.865, Table 6), and the proportion of overall severe AEs was 0.122 (95% CI = 0.027–0.261, Table 6). The most common type of AEs was myeloid suppression (OR = 0.500, 95% CI = 0.236–0.764), and the most common kind of severe AEs was fatigue (OR = 0.039, 95% CI = 0.008–0.086). The details of severe AEs are presented in Table 6.

We observed no significant effect of publication bias on the pooled HR for the median DFS using Egger’s (P = 1.000, Fig. 5A) and Begg’s test (P = 0.464). There was no significant effect of publication bias on the pooled HR for median OS using Egger’s test (P = 0.045, Fig. 5B), but not Begg’s test (P = 0.174). However, using the “trim and fill” analysis, the advantage of adjuvant EBRT over surgery alone remained (HR = 0.362, 95% CI = 0.279–0.471, P < 0.05), which indicated that the unpublished studies had no significant effect on the results.

Table 4
Subgroups analysis comparing adjuvant EBRT versus surgery alone.

| Subgroups    | Disease-free survival | Overall survival |
|--------------|-----------------------|------------------|
|              | Studies included | Patients | Effect model | HR (95%CI) | P       | Studies included | Patients | Effect model | HR (95%CI) | P       |
| Narrow margin| 4 467            | Fixed | 0% | 0.37(0.23–0.60) | <0.001 | 4 467 | Fixed | 0% | 0.32(0.19–0.55) | <0.001 |
| MVI          | 3 229            | Fixed | 0% | 0.28(0.19–0.44) | <0.001 | 3 229 | Fixed | 30% | 0.28(0.17–0.46) | <0.001 |
| PVTT         | 2 113            | Fixed | 0% | 0.40(0.28–0.57) | <0.001 | 2 113 | Fixed | 0% | 0.42(0.30–0.60) | <0.001 |
| Prospective study | 4 306  | Fixed | 0% | 0.36(0.24–0.52) | <0.001 | 4 306 | Fixed | 23% | 0.36(0.23–0.55) | <0.001 |
| Retrospective study | 4 427   | Fixed | 0% | 0.36(0.26–0.49) | <0.001 | 4 427 | Fixed | 0% | 0.37(0.26–0.51) | <0.001 |

Notes: HR, hazard ratio; CI, confidence interval.

Discussion
Recurrence is still the bottleneck of HCC management, but there is no consensus over the role of adjuvant treatment in these patients [1–3]. To the best of our knowledge, this was the first systematic review evaluating the feasibility and efficacy of adjuvant EBRT following hepatectomy for HCC. A total of 10 studies enrolling 974 patients were eligible for this study, which included three RCTs, one phase II trial, and one retrospective comparative study using PSM. The results showed that adjuvant EBRT decreased the risk of recurrence and conferred oncological benefit for HCC patients receiving hepatectomy, but without increasing severe radiation-related AEs. Our results suggest that adjuvant EBRT can be considered for a selected subset of HCC patients, such as combined with narrow margin, MVI, and PVTT.

MVI is generally regarded as the primary origin of intrahepatic recurrence [33,34], and is one of the most important adverse prognostic risk factors. MVI has been a key concern in the recent decade with the incidence rates ranging from 15.0% to 57.1% [35], although there is no clear consensus on its definition. Wang et al [22] first identified that adjuvant EBRT can result in better oncological outcomes for patients with MVI compared with adjuvant TACE or surgery alone. This systematic review included three studies that were conducted on patients with MVI, and the pooled HR for median DFS and OS were both in favor of adjuvant EBRT over surgery alone (P < 0.001 for both), regardless of conventional fractions or SBRT. Hence, patients with MVI may potentially benefit from adjuvant EBRT.

Narrow margin is also one of the most important risk factors for recurrence and adverse prognosis [36,37], although the optimal margin distance is still not clear. With the advances in surgical technique, increasingly complex hepatectomy including mesohepatectomy are being carried out worldwide [4]. The extended indications for hepatectomy have conferred oncological benefit compared with conservative therapy; however, this also results in increased risk of narrow margin and recurrence [5,6]. In a prospective randomized study, Yu et al [17] first reported the feasibility and safety of adjuvant EBRT for centrally located HCC receiving narrow-margin hepatectomy, although significant between-group difference was not observed in terms of DFS and OS (P > 0.05 for both). In the present systematic review, four studies were conducted on patients with narrow margin, and meta-analysis identified the advantage of adjuvant EBRT, both with respect to DFS and OS (P < 0.001 for both). Consequently, adjuvant EBRT may also be considered for patients with narrow margin.

HCC with PVTT, staged at BCLC-C, was earlier considered as a contraindication for hepatectomy [2]. Chen et al [38] first identified the feasibility of surgical resection for patients with PVTT. Subsequent studies and a meta-analysis have confirmed the oncological benefit of hepatectomy plus thrombectomy over conservative therapy [39]. Nonetheless, the median DFS in patients with PVTT was significantly shorter than those without PVTT, and the 2-year DFS rate was as low as 16.1% [40]. In an open-label randomized RCT, Sun et al [18] reported that the median DFS of
PVTT patients receiving adjuvant IMRT was significantly longer than those receiving partial hepatectomy plus thrombectomy (9.1 ± 1.6 months vs 4.1 ± 0.5 months, P < 0.05); in addition, the former group also showed longer OS (18.9 ± 1.8 months vs 10.8 ± 1.3 months, P < 0.05). In the current systematic review, two studies included patients with PVTT, and the pooled HR for median DFS and OS were both in favor of adjuvant EBRT to surgery alone (P < 0.05 for both). However, in a subgroup analysis of a previous RCT, the survival advantage conferred by adjuvant EBRT was not observed among patients with PVTT type III and IV; this was likely attributable to the occurrence of recurrence or metastasis before adjuvant EBRT. Novel adjuvant modalities such as combi-

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**Table 5**

Pattern of recurrence of HCC in included studies.

| Factors                        | Studies included | Patients | Effect model | I² | OR (95%CI)          | P     |
|-------------------------------|-----------------|----------|--------------|----|--------------------|-------|
| Intrahepatic recurrence       | 5               | 464      | Fixed        | 41%| 0.34(0.23–0.50)     | <0.001|
| Marginal recurrence           | 4               | 345      | Fixed        | 14%| 0.51(0.20–1.29)     | 0.150 |
| Non-marginal recurrence       | 4               | 345      | Fixed        | 23%| 0.50(0.31–0.79)     | 0.003 |
| Single lesion of intrahepatic recurrence | 4 | 370      | Random       | 53%| 1.06(0.50–2.22)     | 0.880 |
| Multiple lesion of intrahepatic recurrence | 4 | 370    | Fixed        | 0% | 0.41(0.22–0.75)     | 0.004 |
| Extrahepatic recurrence       | 5               | 464      | Fixed        | 0% | 0.50(0.26–0.97)     | 0.040 |

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**Fig. 4.** Sensitivity analysis for the pooled disease-free survival and overall survival rates between adjuvant EBRT and surgery alone (A, disease-free survival; B, overall survival).
### Table 6
Treatment-related adverse events of adjuvant external beam radiotherapy.

| Events               | All grade | Grade $\geq$ 3 |
|----------------------|-----------|-----------------|
|                      | Included studies | Participants | Effect model | Proportion (95%CI) | Included studies | Participants | Effect model | Proportion (95%CI) |
| Total                | 6         | 237            | Random       | 0.653 (0.405–0.865) | 7               | 263           | Random       | 0.122 (0.027–0.261) |
| Nausea and vomiting  | 6         | 237            | Random       | 0.167 (0.113–0.229) | 7               | 263           | Fixed        | 0.000 (0.000–0.011)  |
| RILD                 | 6         | 237            | Random       | 0.209 (0.044–0.442) | 7               | 263           | Random       | 0.024 (0.000–0.076)  |
| Myeloid suppression  | 6         | 237            | Random       | 0.500 (0.236–0.764) | 6               | 237           | Fixed        | 0.039 (0.008–0.086)  |
| Fatigue              | 5         | 227            | Fixed        | 0.192 (0.142–0.247) | 6               | 253           | Random       | 0.005 (0.000–0.036)  |
| Abdominal pain       | 3         | 81             | Random       | 0.164 (0.080–0.471) | 3               | 81            | –            | 0.000          |
| Anorexia             | 4         | 176            | Random       | 0.162 (0.047–0.322) | 5               | 202           | Random       | 0.005 (0.000–0.038)  |
| Dermatitis           | 4         | 189            | Random       | 0.122 (0.054–0.208) | 4               | 189           | –            | 0.000          |
| Hypoalbuminemia      | 2         | 109            | Fixed        | 0.081 (0.034–0.142) | 2               | 109           | –            | 0.000          |
| Infections           | 2         | 39             | Fixed        | 0.042 (0.000–0.143) | 2               | 39            | –            | 0.000          |

Notes: RILD, radiation induced liver disease; CI, confidence interval.

**Fig. 5.** Egger’s tests for publication bias (A, disease-free survival; B, overall survival).
nation with systemic treatment should be considered for this population.

TACE is the preferred adjuvant treatment for HCC patients, especially in the East Asia, although international consensus has not been reached [41,42]. Adjuvant TACE for HCC was first reported in 1995 [43], and since then several retrospective and prospective studies have demonstrated its efficacy in preventing recurrence, especially among patients with MVI, narrow margin, and PVTT [44–46]. With the development of RT techniques, adjuvant EBRT has been tried in the management of HCC. However, there is a paucity of studies comparing the anti-recurrence efficacy of adjuvant EBRT versus TACE for HCC. Bai et al [21] first compared the efficacy of adjuvant EBRT versus TACE for patients with PVTT. They found no significant difference between the two groups in terms of DFS or OS (P > 0.05 for both). However, a subsequent study demonstrated the advantage of EBRT among patients with MVI [22]. In the current review, three studies had compared adjuvant EBRT versus TACE, and the pooled HR for the median DFS and OS were both in favor of adjuvant EBRT (P < 0.001 for both). Nonetheless, it is too early to draw a definitive conclusion about the optimal adjuvant treatment for HCC.

Safety is one of the decision-making factors in cancer management. Liver was considered as a contraindication for RT, and radiation-induced liver disease (RILD), regardless of classic or non-classic, is a common and fatal adverse event [47]. Owing to rapid advances in RT techniques (such as 3DCRT, IMRT and SBRT), EBRT has been adopted for treatment of all stages of HCC. In addition, advances in breathing-motion management strategies such as four-dimensional computed tomography, and real-time target tracking and continuous patient position adjustment with robotic treatment couches have also facilitated the application of RT [48]. In the present study, the pooled incidence of total-treatment-related AEs was 65.3%, but the rate of severe AEs was only 12.2%. The top three common AEs were myeloid suppression, RILD, and fatigue, but the corresponding severe rates were 3.9%, 2.4%, and 0.5%, respectively. Notably, no fatal AE related to adjuvant EBRT was reported in the included studies. These findings indicate the feasibility and safety of adjuvant EBRT in the management of HCC.

In addition, radiation-immunity is a growing concern in recent years. Preclinical studies have found that radiation can induce remodeling of the tumor immune microenvironment via multiple mechanisms, such as exosomes and stromal cells [49,50]. In the study by Du et al [51], RT was found to promote HCC immune cloaking through PD-L1 upregulation, which offered theoretical support for the combination of RT and immune checkpoint inhibitors (ICIs). In 2019, Yu et al [52] first identified the survival gain conferred by addition of RT to ICI therapy, which was further confirmed by the subsequent reports [53,54]. Moreover, Sung et al [55] established a mathematical model to simulate the effect of adding RT to ICIs, which was verified in patients with HCC. Considering that local recurrence is still the main mode of treatment failure in HCC, aggressive adjuvant treatment modality, such as RT and ICIs, would be an alternative option.

More consensus can be reached over the role and modalities of adjuvant EBRT. First, adjuvant EBRT can be an option for patients with MVI, narrow margin, or PVTT to decrease recurrence. Second, 4–6 weeks after surgery might be the optimal interval time for adjuvant EBRT. Third, 3D-CRT or IMRT using conventional fractions with total dose of 50–60 Gy was strongly recommended, but SBRT can also be adopted as an alternative option. Fourth, CTV should consist of tumor bed indicated by silver markers, but there is controversy regarding the expand distance. The main trunk and branch of portal vein should also be incorporated in case of PVTT. Last but not the least, organs at risk (OARs) including normal liver, stomach and duodenum, colon, cord, and kidney should be treated with caution.

However, due caution should be exercised while interpreting the results of our study. All the studies included in this review were conducted in China. Thus, the conclusions may not be entirely applicable to Western population because of differences in the pathogenesis between the East and the West. Secondly, almost half of the included studies were retrospective observational studies which would weaken the conclusion of the current study. However, the results of subgroup analysis stratified by study design (retrospective and prospective) were consistent. Besides, there were apparent differences among the included studies with respect to study population (MVI, narrow margin, or PVTT) and EBRT techniques (3DCRT, IMRT, or SBRT), although no significant heterogeneity was found among the included studies in this respect. Moreover, the results of corresponding subgroup analysis were consistent with the overall results. Finally, the long-term survival benefit of adjuvant EBRT has not been verified with unimproved DFS and OS at 5-year (P > 0.05 for both), which should weaken the clinical value of adjuvant EBRT.

Conclusion

The available evidence suggests that adjuvant EBRT can be considered for HCC patients, especially those with MVI, narrow margin, or PVTT. However, more attention should be paid to the management of adjuvant EBRT, such as RT modality, fraction/dose, and delineation of CTV. Considering the promising results of adjuvant EBRT for HCC, international multi-center RCTs with larger sample size are required to obtain more definitive evidence.

Disclosure

The author reports no conflicts of interest in this work.

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Author contributions

Lei Wang, Lu Qiu, and Qiao Ke acquisition of data, analyzing and interpretation of data, drafting the article; Hongbing Ji revising the article; Junxin Wu designing and guiding the study.

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