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Review Article

Separation surgery followed by stereotactic ablative radiotherapy for metastatic epidural spinal cord compression: A systematic review and meta-analysis for local progression rate

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ABSTRACT

Introduction: Spinal metastasis is the most common metastatic skeletal disease in cancer patients. Metastatic epidural spinal cord compression (MESCC), which occurs in 5–14% of cancer patients, is an oncological emergency because it may cause a permanent neurological deficit. Separation surgery followed by stereotactic ablative radiotherapy (SABR), so-called "hybrid therapy," has shown effectiveness in local control of spinal metastasis and has become an integral treatment option for patients with MESCC. Therefore, we performed a meta-analysis and meta-regression analysis to clarify the local progression rate of hybrid therapy and the risk factors for local progression.

Methods: We searched PubMed, EMBASE, Scopus, Cochrane Library, and Web of Science databases from inception to December 2021. Meta-analyses of proportions were used to analyze the data using a random-effects model to calculate the pooled 1-year local progression rate and confidence interval. Subgroup analyses were performed using meta-analyses of odds ratio (OR) for comparisons between groups. We also conducted a meta-regression analysis to identify the factors that caused heterogeneity.

Results: A total of 661 patients from 13 studies (10 retrospective and 3 prospective) were included in the final meta-analysis. The quality of the included studies assessed using the Newcastle − Ottawa scale ranged from poor to fair (range, 4–6). The pooled local progression rate was 10.2 % (95 % confidence interval [CI], 7.8–12.8 %; $I^2 = 30$ %) and 13.7 % (95 % CI, 9.3–18.8 %; $I^2 = 55$ %) at postoperative 1 and 2 years, respectively. The subgroup analysis indicated that patients with a history of prior radiotherapy (OR, 5.14; 95 % CI, 1.71–15.51) and lower radiation dose per fraction (OR, 4.57; 95 % CI, 1.88–11.13) showed significantly higher pooled 1-year local progression rates. In the moderator analysis, the 1-year local progression rate was significantly associated with the proportion of patients with a history of prior radiotherapy ($p = 0.036$) and those with colorectal cancer as primary origin ($p < 0.001$).

Conclusions: The pooled 1-year local progression rate of hybrid therapy for MESCC was 10.2%. In subgroup and moderator analyses, a lower radiation dose per fraction, history of prior radiotherapy, and colorectal cancer showed a significant association with the 1-year local progression rate.

1. Introduction

Spinal metastasis is the most common metastatic skeletal disease in cancer patients [1,2]. Metastatic epidural spinal cord compression (MESCC), which occurs in 5–14 % of cancer patients, is an oncological emergency because it may cause a permanent neurological deficit [3]. En bloc resection has lost its role in spinal metastasis because it has no positive effect on the oncologic outcomes of spinal metastasis [4]. Previous studies have shown that decompressive surgery and radiotherapy, the two main treatment options for patients with MESCC, can improve

Abbreviations: MESCC, metastatic epidural spinal cord compression; cEBRT, conventional external beam radiation therapy; SABR, stereotactic ablative radiotherapy; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MOOSE, Meta-Analysis of Observational Studies in Epidemiology; MRI, magnetic resonance imaging; CT, computed tomography; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; Gy, Gray.

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clinical outcomes in patients with spinal metastasis [5,6]. Although conventional external beam radiation therapy (cEBRT) has been widely used for radiotherapy, the biologically effective dose (BED) is limited due to the adjacent spinal cord when cEBRT is applied to spinal metastasis. Therefore, the effectiveness of cEBRT is highly dependent on primary cancer [6–8].

In contrast to cEBRT, stereotactic ablative radiotherapy (SABR) delivers a higher BED to target tissues while minimizing the dose exposure to normal tissue, including the spinal cord [9–12]. Due to its effectiveness, regardless of tumor histology, SABR has become a game-changer in spinal metastasis treatment [13,14]. SABR improves the outcomes of radiotherapy, but it has also changed the extent of surgical treatment for MESCC and allows separation surgery to be performed [15]. In separation surgery, tumor resection is limited to decompressing the spinal cord and creating a gap between the spinal cord and the tumor for the safe application of SABR [16]. Separation surgery followed by postoperative SABR, the so-called "hybrid therapy," has been shown to be safe and effective in previous studies and has become an integral treatment option for patients with MESCC [6,17–19].

Although previous studies on hybrid therapy have reported a good local control rate of 84 % or greater in the postoperative 1-year [20], information is still limited due to the lack of large-scale studies and considerable heterogeneity between the published studies. Therefore, we conducted this systematic review and meta-analysis to clarify the local progression rate of hybrid therapy at postoperative 1 and 2 years and to identify the risk factors associated with local progression.

2. Materials and methods

2.1. Study design

The protocol for the current meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021289134). This study was conducted following the Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) guidelines and meta-Analysis of Observational Studies in Epidemiology (MOOSE) standards [21,22].

2.2. Study identification

Two reviewers (D.H.K. and S.Y.C.) independently performed a systematic search of electronic databases, including PubMed, EMBASE, Scopus, Cochrane Library, and Web of Science, from inception until December 2021. The search strategy was designed to maximize the sensitivity of the search using a combination of the following keywords: (((spinal metastasis) OR (spinal metastases) OR (vertebral metastasis) OR (vertebral metastases)) AND ((separation surgery) OR (hybrid therapy) OR (decompressive surgery) OR (decompression) OR (intralesional resection) OR (subtotal resection)) AND ((radiotherapy) OR (radiosurgery) OR (stereotactic body radiotherapy) OR (SBRT) OR (stereotactic ablative radiotherapy) OR (SBRT))). The detailed contents of the search strategy are presented in Appendix 1. Furthermore, the reference lists of the identified studies were manually searched to identify potentially relevant citations. We used Covidence (Veritas Health Innovation, Melbourne, Australia) to remove duplicates and perform an title and abstract screening, full-text review, and selection of studies for quantitative analysis. Any disagreement between the two reviewers was resolved by discussing it with a third reviewer (B.S.C.). Studies that were not published in English were excluded.

2.3. Selection of studies

The studies were selected according to the PRISMA recommendations by two independent reviewers (D.H.K, S.Y.C.). All studies involving patients with spinal metastases who underwent separation surgery combined with early postoperative SABR (hybrid therapy) were included. Conference abstracts or poster abstracts that met the inclusion criteria were also included to maximize the sensitivity of the eligible gray literature. Studies were excluded if they did not have information on the number of local progressions at 1-year of follow-up after hybrid therapy. Duplications were also excluded, as were case series of fewer than five patients, database studies incorporating primarily reported data, studies including data from the same database, and studies without abstracts, letters, and expert opinions.

2.4. Quality assessment

The quality of each study was assessed using the Newcastle − Ottawa scale for nonrandomized studies by four independent researchers (D.H.K., S.Y.C, H.M.K., and S.H.H.). Funnel plots and Egger's test were used to assess publication bias between studies when at least five studies were included for pooling. The detailed content of the quality assessment is provided in Appendix 2.

2.5. Data extraction and outcomes

Two reviewers (D.H.K. and S.Y.C.) extracted data from each included study. Data extracted included the first author, year of publication, country of origin, age, sex, number of patients showing local progression at 1-year and 2-year follow-up after hybrid therapy, number of total patients, proportion of radioresistant primary tumors, proportion of primary tumor histology, proportion of patients with prior radiotherapy in spinal metastasis, proportion of patients with high-grade epidural disease (defined as Bilsky grade 2 or 3) preoperatively and postoperatively, radiation scheme of SABR, and study design. The primary outcome of this study was the 1-year cumulative incidence of local progression after hybrid therapy. As revealed on magnetic resonance imaging (MRI) or computed tomography (CT), local progression was defined as tumor progression within the treated volume. Another outcome of interest was the 2-year cumulative incidence of local progression after hybrid therapy.

2.6. Statistical analysis and synthesis

The study characteristics and patient demographics were summarized with descriptive synthesis. Because most of the included studies did not report outcome data for a control group (e.g., separation surgery alone), meta-analyses of proportions were used to analyze the data to calculate the pooled 1-year local progression rate and confidence interval using a random-effects model. The χ^2 and I^2 analyses were used to assess statistical heterogeneity, in which I^2 values greater than 50 % were suggested as indicators of the presence of heterogeneity. If substantial heterogeneity was found ($I^2 > 50$ %), a random-effects model was used; otherwise, a fixed-effects model was used. Subgroup analyses were performed using meta-analyses of odds ratios (OR) for comparison between the higher dose per fraction group and lower dose per fraction group and between the prior radiotherapy group and no prior radiotherapy group. To identify risk factors that affect local progression, univariate meta-regression was used to identify potential heterogeneity between studies arising from several factors, including the proportion of patients with radioresistant primary tumors, proportion of patients with each type of primary tumor, proportion of patients with a history of prior radiotherapy in spinal metastatic lesions, proportion of patients with preoperative and postoperative high Bilsky grade (grade 2 or 3), median value of total radiation dose, number of fractions, and median value of radiation dose per fraction. Publication bias assessment was performed using funnel plots and Egger tests. All statistical analyses were performed with R version 4.1.2 (meta and metafor packages). Two-sided p-value <0.05 was considered statistically significant.

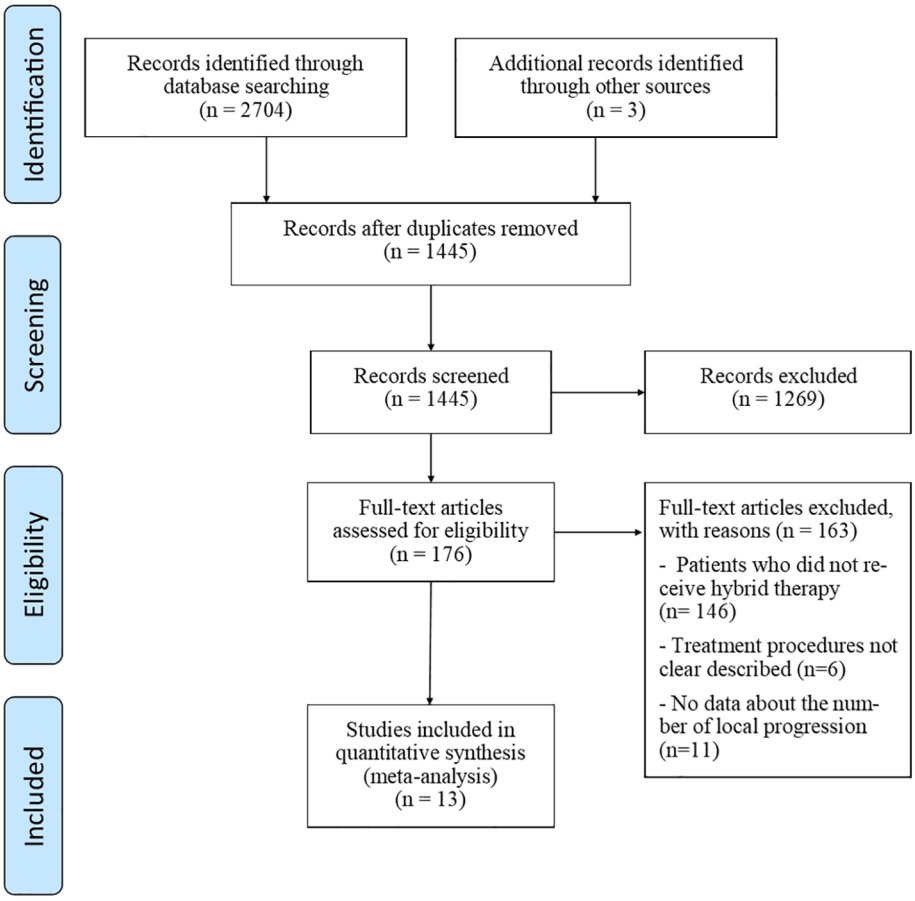

Fig. 1. PRISMA flow diagram.

Table 1
The characteristics of selected studies.

Author & Year	Country	Study design	Inclusion Period	Evaluation method of local progression	Median age at surgery	No. of total patients	No. of 1-yr local progression	No. of 2-yr local progression
Moulding et al. 2010	USA	Retrospective	2003–2008	MRI and/or CT myelography	53.2	21	2	4
Laufer et al. 2013	USA	Retrospective	2002–2011	MRI and/or CT myelography	48.9	186	27	32
Bate et al. 2015	USA	Retrospective	2007–2011	MRI	60	21	2	–
Barzilai et al. 2018	USA	Prospective	2013–2016	No mention	61.4	111	4	5
Ito et al. 2018	Japan	Retrospective	2013–2017	MRI and/or CT	62	28	7	7
Hu et al. 2020	China	Retrospective	2013–2018	MRI and CT	54.9	26	2	2
Redmond et al. 2020	USA	Prospective	2013–2017	MRI and/or CT	63	35	3	3
Xiaozhou et al. 2020	China	Retrospective	2015–2018	MRI and CT	56.7	13	1	1
Cao et al. 2021	China	Retrospective	2013–2020	No mention	58.7	26	2	6
Gong et al. 2021	China	Retrospective	2016–2019	MRI	55.1	35	6	7
Ito et al. 2021	Japan	Prospective	2017–2019	MRI or CT	63	33	4	7
Pennington et al. 2021	USA	Retrospective	2009–2019	MRI	60.5	97	10	12
Xu et al. 2021	China	Retrospective	2017–2020	MRI, CT, and PET/CT	56.3	29	4	–

3. Results

3.1. Systematic review

A total of 2704 studies were initially identified from a database search of PubMed, EMBASE, Scopus, the Cochrane Library, and Web of Science. Three studies were identified by searching the reference lists of the relevant articles. After removing duplicates, the titles and abstracts of 1445 studies were screened. Of these, 1269 were excluded as irrelevant and full-text reviews were performed on the remaining 176 studies. Thirteen studies were included in the final meta-analysis based on the inclusion and exclusion criteria (Fig. 1).

3.2. Study and patient population characteristics

A total of 661 patients from 13 studies were included in the final

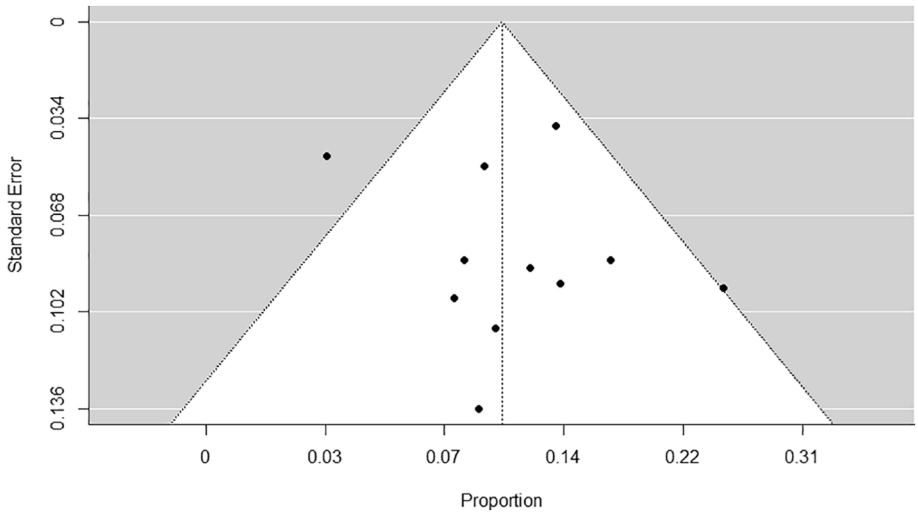

Fig. 2. The funnel plot shows the distribution of effect estimates (1-year local progression rate) plotted against standard error.

Table 2
The radiation schemes of postoperative SABR.

Author & Year	Time to SABR after surgery	Radiation scheme
Moulding et al. 2010	Mean 43.9 days	24 Gy in 1 fraction: 16 cases 18–21 Gy in 1 fraction: 5 cases
Laufer et al. 2013	Median 6.4 weeks	24 Gy in 1 fraction: 40 cases 24–30 Gy in 3 fractions: 37 cases 18–36 Gy in 5–6 fractions: 109 cases
Bate et al. 2015	–	22 Gy in 1 fraction: 9 cases 20 Gy in 1 fraction: 2 cases 16 Gy in 1 fraction: 3 cases 20 Gy in 2 fractions: 1 cases 27 Gy in 3 fractions: 3 cases 30 Gy in 5 fractions: 3 cases
Barzilai et al. 2018	Median 20 days	24 Gy in 1 fraction: 17 cases 27 Gy in 3 fractions: 70 cases 30 Gy in 5 fractions: 24 cases
Ito et al. 2018	Median 4 weeks	24 Gy in 2 fractions
Hu et al. 2020	Median 6 weeks	25–40 Gy in 3–5 fractions
Redmond et al. 2020	No more than 16 weeks	30 Gy in 5 fractions
Xiaozhou et al. 2020	10–20 days	24 Gy in 1 fraction 18–36 Gy in 3–6 fractions
Cao et al. 2021	Within 20–30 days	24–30 Gy in 3 fractions
Gong et al. 2021	Median 5.6 weeks	25–40 Gy in 3 or 5 fractions
Ito et al. 2021	Median 4 weeks	24 Gy in 2 fractions
Pennington et al. 2021	–	30 Gy in 5 fractions: 34 cases 27 Gy in 3 fractions: 18 cases 25 Gy in 5 fractions: 16 cases 24 Gy in 3 fractions: 7 cases 21 Gy in 3 fractions: 8 cases 24 Gy in 2 fractions: 7 cases Other: 7 cases
Xu et al. 2021	Within 30 days	24–30 Gy in 3–4 fractions

meta-analysis, with a median age of 48.9 to 63 years. All studies were observational cohort, case-control, or noncomparative studies (Table 1). Ten studies were retrospective, including a total of 482 patients, and three studies were prospective studies of 179 patients. Eleven studies reported the sex proportion of included patients, and of these, 58 % were male [18,19,23–31]. Six studies were conducted in the United States, five in China, and two in Japan. The quality of the included studies assessed using the Newcastle – Ottawa scale ranged from poor to fair (range, 4–6). The funnel plot showing the distributions of the effect estimate (1-year local progression rate) plotted against standard error was symmetrical with a p-value of 0.537 in Egger's test (Fig. 2).

3.3. Separation surgery and postoperative SABR

All included patients underwent decompressive surgery to provide a circumferential safe margin between the spinal cord and the tumor for postoperative SABR, which is the core concept of separation surgery. The precise term "separation surgery" was not used in two studies when describing the surgical method [23,27]. Instead, circumferential decompression or decompressive surgery was performed to create tumor-free space around the spinal cord for postoperative SABR. In two studies comparing moderate to aggressive resection, both groups were considered to have undergone separation surgery [28,30]. The extent of surgical decompression was described using the Bilsky grade in six studies [6,18,25,28–30]. Five studies [6,18,28–30] presented data on preoperative Bilsky grade and five studies [6,18,25,29,30] presented data on postoperative Bilsky grade.

These studies used various SABR protocols, as detailed in Table 2. Eleven studies [6,18,19,23–30] described the contouring method for postoperative SABR, including gross tumor volume, clinical target volume, and planning target volume. Six studies [19,23–25,27,29] specified maximum dose constraints for the spinal cord with a range of 11.0–14 Gray (Gy).

3.4. Primary outcome: 1-year local progression

All included studies reported the number of patients with local progression in 1-year after hybrid therapy. The meta-analysis showed that the pooled 1-year local progression rate was 10.2 % (95 % confidence interval [CI], 7.8–12.8 %; I^2 = 30 %) (Fig. 3A). Two studies compared the 1-year local progression rate between groups with and without a history of prior radiotherapy [26,30]. The pooled 1-year local progression rates were 33.3 % (7/21) and 8.7 % (11/126) for patients with and without prior radiotherapy, respectively. The heterogeneity of the included studies was low ($I^2 = 0$ %, p = 0.82). A fixed-effects model showed 5.14 times higher odds of local progression in the prior radiotherapy group (OR, 5.14; 95 % CI, 1.71–15.51) (Fig. 3B).

Three studies compared the 1-year local progression rates between the lower dose and higher dose per fraction groups [6,23,26]. In a study by Molding et al., patients were divided into an 18–21 Gy in single fraction group (lower dose) and a 24 Gy in single fraction group (higher

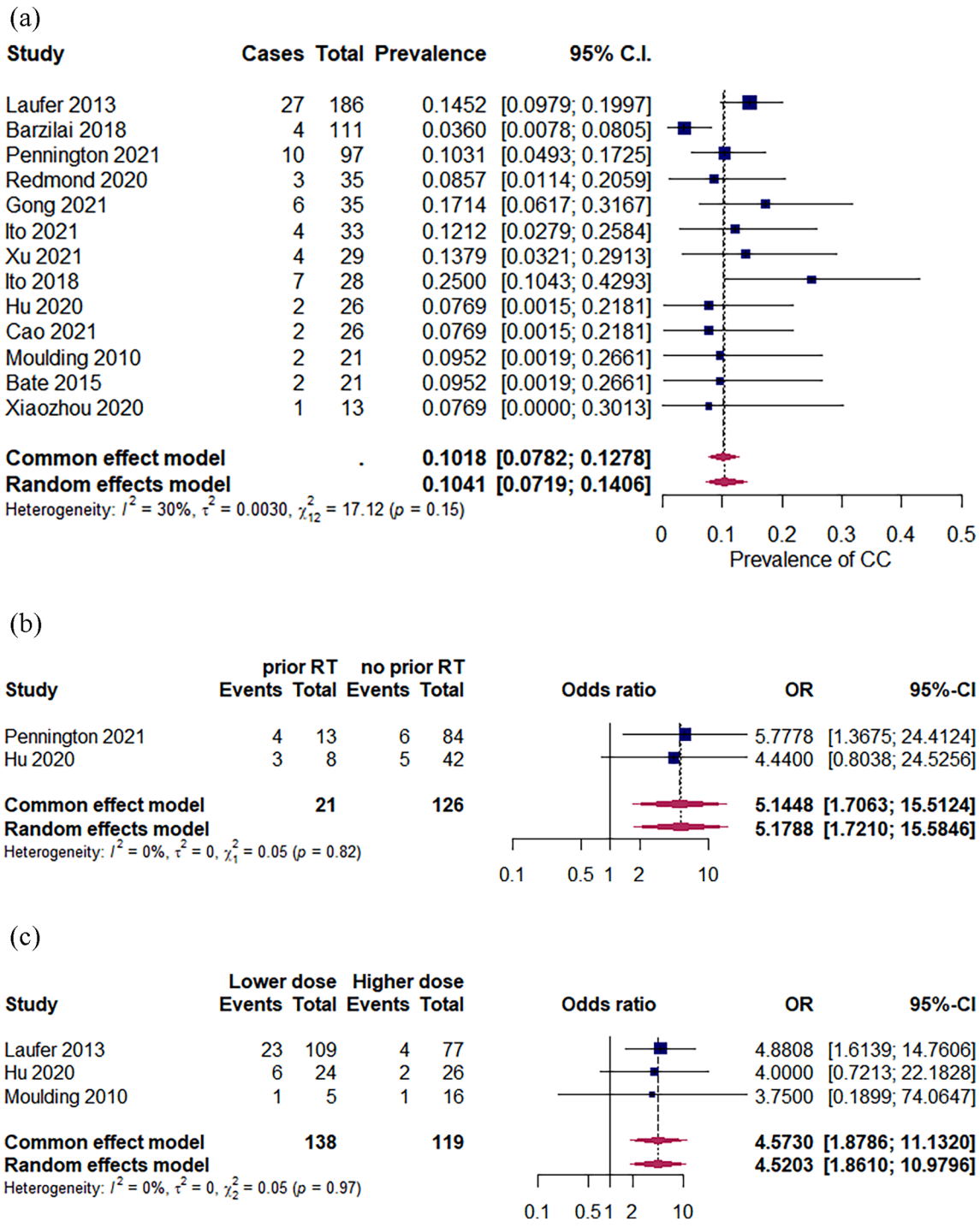

Fig. 3. A) Forest plot of 13 studies reporting 1-year local progression following hybrid therapy for spinal metastases. Fixed-effect modeling of the pooled local progression rate at 1-year was used for the meta-analysis of proportions with 95% confidence intervals. B) Comparison of the 1-year local progression rate between the group with a history of prior radiotherapy in metastatic lesions and no prior radiotherapy group in the two studies. C) Comparison of the 1-year local progression rate between the higher dose per fraction group and the lower dose per fraction group in three studies.

dose). Laufer et al. compared 30 Gy in 5 to 6 fractions (lower dose) with 24 Gy in single fraction and 27 Gy in 3 fractions (higher dose). In a study by Hu et al., 48 Gy in 12 fractions (lower dose) and 35 Gy in 5 fractions (higher dose) were compared. In Laufer's study, 27 Gy in 3 fractions group and 30 Gy in 5 to 6 fractions group received similar delivered dose of BED10 (51.2 Gy vs 48 Gy), but 30 Gy in 5–6 fractions group showed lower LC rate in 1 year after radiotherapy than 27 Gy in 3 fractions group (78.9 % vs 94.8 %; p = 0.002) [6]. In Hu's study, 48 Gy in 12 fractions group received higher delivered dose of 67.2 Gy (BED10) than 35 Gy in 5 fractions group of 59.50 Gy (BED10), but 48 Gy in 12 fractions group, although not a significant difference, showed lower LC rate in 1 year after radiotherapy than 35 Gy in 5 fractions group (75 % vs 92.3 %; p = 0.09) [26]. The pooled 1-year local progression rates were 21.7 % (30/138) and 5.9 % (7/119) for the low- and higher dose groups, respectively. The heterogeneity of the included studies was low (I^2 = 0 %, p = 0.97). A fixed-effects model showed 4.57 times higher odds of local progression in the lower dose group than in the higher dose group (OR, 4.57; 95 % CI, 1.88–11.13) (Fig. 3C).

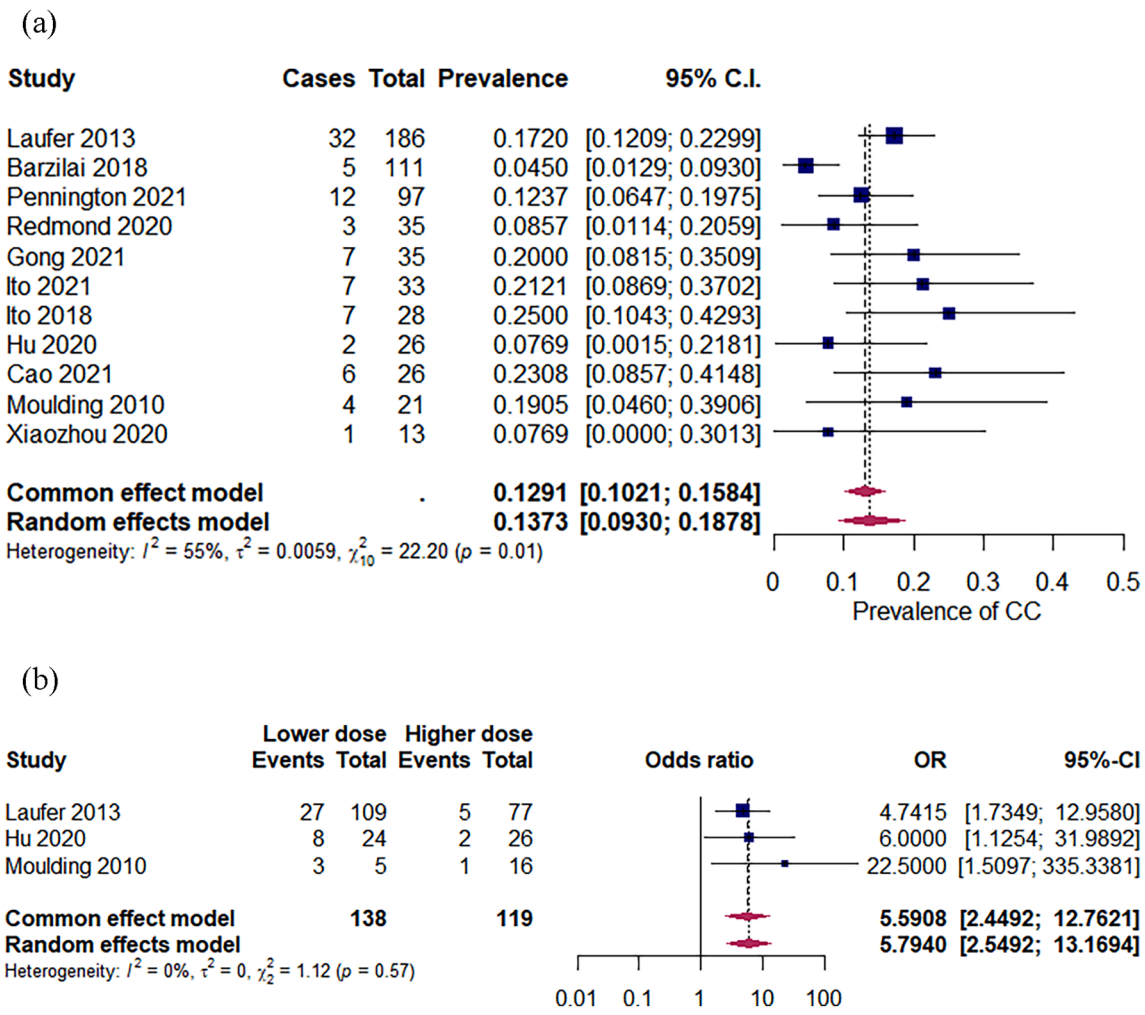

Fig. 4. A) Forest plot of 11 studies reporting 2-year local progression following hybrid therapy for spinal metastases. Random-effects modeling of the pooled local progression rate at 1-year was used for the meta-analysis of proportions with 95% confidence intervals. B) Comparison of the 2-year local progression rate between the group with a history of prior radiotherapy in metastatic lesions and no prior radiotherapy group in the two studies.

3.5. Secondary outcome: 2-year local progression

The meta-analysis showed that the pooled 2-year local progression rate was 13.7 % (95 % CI, 9.3–18.8 %; $I^2 = 55$ %) (Fig. 4A). The 2-year local progression rate was compared between the lower and higher dose per fraction groups in three studies [6,23,26]. The two groups were divided as described above. The pooled 2-year local progression rates were 27.5 % (38/138) and 6.7 % (8/119) for the lower dose and higher dose groups, respectively. The heterogeneity of the included studies was low ($I^2 = 0$ %, p = 0.57). A fixed-effects model showed 5.59 times higher odds of local progression in the lower dose group (OR, 5.59; 95 % CI, 2.45–12.76) (Fig. 4B).

3.6. Moderator analysis

Seven of the 13 studies reported the proportion of patients with a history of radiotherapy for spinal metastatic lesions [6,18,25–27,29,30]. The association between the proportion of patients with a history of prior radiotherapy and the 1-year local progression rate was statistically significant (p = 0.036) (Fig. 5A). Nine of the 13 studies reported the proportion of patients with primary tumor histology [6,18,19,23,25,26,28–30]. The proportion of radiosensitive and radioresistant tumors showed no significant association with the 1-year local progression rate. Among all primary tumor histology, only colorectal cancer showed significant association between the proportion of patients with that origin and the 1-year local progression rate ($p < 0.001$) (Fig. 5B). A total of 35 patients with spinal metastasis of colorectal origin were included in the moderator analysis. Only two studies specified the local progression rate among included patients with spinal metastasis of colorectal origin. Laufer reported that 1 out of 15 patients with spinal metastases of colorectal origin had local recurrence [6], and Pennington reported 3 out of 4 patients until the last follow-up [30]. Other factors did not show a significant association with the 1-year local progression rate.

4. Discussion

The current systematic review and meta-analysis showed that the pooled 1-year local progression rate was 10.2 % (95 % CI, 7.8–12.8 %; $I^2 = 30$ %) following hybrid therapy (separation surgery with postoperative SABR) for spinal metastasis. The pooled 2-year local progression rate was 13.7 % (95 % CI, 9.3–18.8 %; $I^2 = 55$ %), showing little difference from the pooled 1-year local progression rate. This initial steep drop in local control in the first 1-year followed by a plateau in local control in the second 1-year implies that the initial response to SABR is important for determining the patient's local control of spinal metastasis.

In the subgroup analysis, the pooled 1-year local progression rate was higher in the lower dose group than in the higher dose group (21.7 % vs 5.9 %). A fixed-effects model showed 4.57 times higher odds of

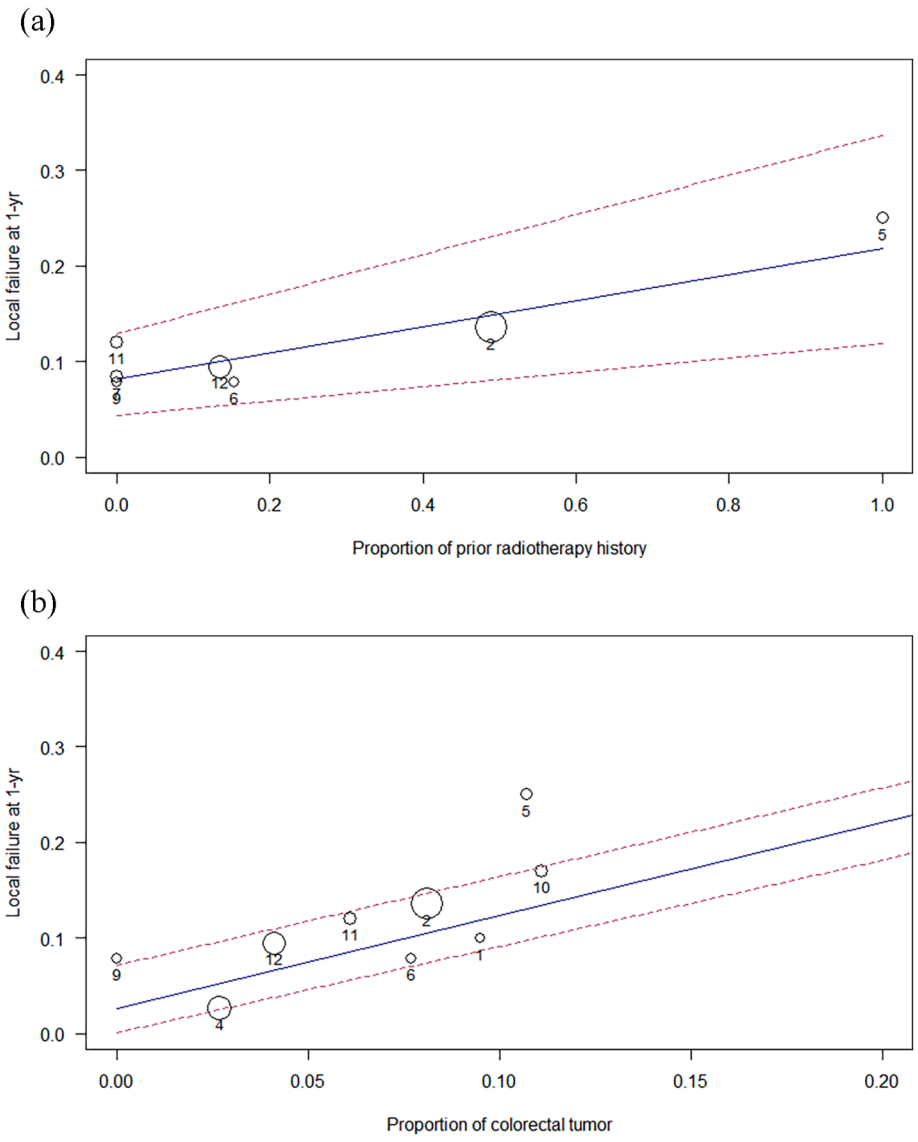

Fig. 5. Moderator analysis showing univariate meta-regression of local progression at 1 year following hybrid therapy versus A) the proportion of patients with a history of prior radiotherapy and B) the proportion of colorectal cancer origin in each study. Each dot indicates an individual study, the solid line shows the regression prediction, and the dotted lines show the 95 % confidence intervals.

showing local progression in the lower dose group (OR, 4.57; 95 % CI, 1.88–11.13). In Laufer and Hu's studies, higher dose per fraction group and lower dose per fraction group showed similar delivered dose of BED10, but lower dose per fraction group showed higher local progression rate in 1 year after radiotherapy than higher dose per fraction group [6,26]. In both studies, SABR was performed on the clinical target volume covering the microscopic extension and the planning target volume covering 2–3 mm more. Therefore these findings suggest the existence of minimum dose which can achieve ablation of tumor cells regardless of radioresistance, and dose per fraction should be higher than that minimum dose to be effective for local control of spinal metastasis. These results are echoed by previous studies showing that local control of SABR in spinal metastases appears to improve with single-fraction schedule, but decreases with multiple-fraction schedules [32]. Yamada et al. also showed that local control was improved with single-fraction radiosurgery dose escalation to 24 Gy [33]. Radioresistant tumors, such as sarcoma or renal cell carcinomas, are believed to require a higher radiation dose per fraction to overcome the intrinsic radioresistance of tumor cells [34,35].

But, we may have to increase the number of the fraction size of SBRT in cases wherein the tumor is adjacent to the spinal cord. Increasing fractionation makes it possible to escalate the minimum dose delivered to a gross tumor which can attribute local control. The previous studies indicated that higher doses in the same fraction scheme showed higher 2-years local control rate [36,37]. We concluded that the degree of separation obtained after separation surgery and the resulting maximum permissible dose for residual tumor not exceeding spinal cord dose tolerance are the main factors that determine the fraction of the post-operative SBRT scheme, and after deciding fraction, it is important for local control to give as much dose per fraction as possible.

Subgroup analysis also showed that a history of prior radiotherapy for spinal metastatic lesions was associated with a higher local 1-year local progression rate. The group of patients with a history of prior radiotherapy had a higher pooled 1-year local progression rate (33.3 % vs 8.7 %) and showed higher odds of 1-year local progression (OR, 5.14; 95 % CI, 1.71–15.51) than their counterparts. In the moderator analysis, a history of prior radiotherapy showed a significant association with the 1-year local progression rate. These findings are consistent with those of previous studies, which showed that patients with a history of prior radiotherapy for spinal metastatic lesions showed a higher local

recurrence rate [38,39]. The reradiation therapy of spinal metastases with a history of previous irradiation was thought to be challenging due to radiation dose limitation, which is associated with structural instability, such as vertebral body fracture and injury to the organ at risk, such as the spinal cord. A previous randomized trial showed the limited therapeutic impact of cEBRT as reradiation, with a 2-month overall response rate of 45–51 % and a complete response rate of only 11–14 % [40]. In the case of SABR as the reradiation, a systematic review article reported that spinal SABR achieved a 1-year local control rate of 76 % [41]. Our results are consistent with those of previous studies indicating that postoperative SABR for MESCC as re-irradiation was effective but showed relatively inferior outcomes compared with SABR as the first irradiation [38,42].

Among the various types of primary cancer, only colorectal cancer metastases showed a significant association with the 1-year local progression rate in our meta-analysis. Several previous studies have reported a higher local recurrence of spinal metastases of colorectal origin [30,38,43]. Previous studies have shown that SABR achieves fair local control even for spinal metastasis of radioresistant tumors, including melanoma, sarcoma, thyroid cancer, and renal cell carcinoma [44–47]. However, current results suggest that local control of spinal metastases in colorectal cancer is more difficult than that in other primary cancers.

Although the reasons for such worse outcomes in colorectal cancer are unclear, metastases from colorectal cancer have been reported to contain large amounts of hypoxic cells compared with other primary cancers [48], which can cause radioresistance [49–51]. In other clinical studies, pulmonary oligometastases of colorectal cancer had a lower local control rate after SABR than other primary cancers [52–54]. However, several studies have shown a significant positive effect of higher radiation doses on the local control rate of pulmonary oligometastases in colorectal cancer [54–58]. Therefore, spinal metastases of colorectal cancer require a higher radiation dose for successful local control than those of other primary cancers. If a higher radiation dose is limited to protect organs at risk, such as the spinal cord, the use of bevacizumab, which showed a clinical synergistic effect with SABR on pulmonary oligometastasis from colorectal cancer, can be considered [59].

5. Limitations

The current meta-analysis had several limitations. First, direct comparison between hybrid therapy and other treatment was nearly impossible, because the number of studies that compared the local progression rate between hybrid therapy and other treatments are very limited. In the scope of our project, it was difficult to conduct subgroup analysis comparing hybrid therapy with other treatments because there were only single studies comparing it directly with other treatments. Among included studies, one study showed direct comparison of LC rate between hybrid therapy and SABR alone [24], another showed comparison between hybrid therapy and total en bloc spondylectomy [18], and the other showed comparison between hybrid therapy and piecemeal spondylectomy [31]. Further analysis will become possible if additional studies that directly compare hybrid therapy with the others are published in the future. Our subgroup analysis also included two or three studies, which could carry the possibility of confounding bias. Second, the quality of the included studies assessed by the Newcastle – Ottawa scale ranged was not good (range poor to fair), which should be considered when interpreting the results. Third, the definition of local progression is loose in included studies and may not represent clinical progression. Definitions were described specifically in 11 studies as radiological progression on MRI, CT, or CT myelography, but not in two studies [18,19]. If these two studies use perfusion scans as additional information to determine progression the included data could overestimate the local progression. These discrepancies between studies may have affected the rate of local progression. Fourth, in general, the moderator analysis should include at least 10 studies for each moderator, but our moderator analysis included six to eleven studies for each moderator. Therefore, caution should be taken when generalizing the results, because unidentified factors that were not measured in our moderator analysis could be responsible for this result. Despite these limitations, this study is the first meta-analysis to show the pooled 1-year local progression rate of hybrid therapy (separation surgery with postoperative SABR) for spinal metastases.

6. Conclusion

The current meta-analysis highlights that the pooled 1-year local progression rate of hybrid therapy (separation surgery with postoperative SABR) for spinal metastases was 10.2 % (95 % CI, 7.8–12.8 %; $I^2 = 30$ %). In the subgroup and moderator analyses, low radiation dose per fraction, history of prior radiotherapy, and colorectal cancer as primary cancer showed a significant association with the 1-year local progression rate.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This study did not require any variation in patient treatment, and no formal approval of the ethics committee was required. All processes performed in this study followed the ethical standards of the author's institution and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbo.2022.100450.

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