







Radiation therapy compared to radical prostatectomy as first-line definitive therapy for patients with high-risk localised prostate cancer: An updated systematic review and meta-analysis

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ABSTRACT

Objective: To present an update of the available literature on external beam radiation therapy (EBRT) with or without brachytherapy (BT) compared to radical prostatectomy (RP) for patients with high-risk localised prostate cancer (PCa).

Methods: We conducted a systematic review and meta-analysis of the literature assessing the survival outcomes in patients with high-risk PCa who received EBRT with or without BT compared to RP as the first-line therapy with curative intent. We queried PubMed and Web of Science database in January 2021. Moreover, we used random or fixed-effects meta-analytical models in the presence or absence of heterogeneity per the I^2 statistic, respectively. We performed six meta-analyses for overall survival (OS) and cancer-specific survival (CSS).

Results: A total of 27 studies were selected with 23 studies being eligible for both OS and CSS. EBRT alone had a significantly worse OS and CSS compared to RP (hazard ratio [HR] 1.38, 95% confidence interval [CI] 1.16–1.65; and HR 1.55, 95% CI 1.25–1.93). However, there was no difference in OS (HR 1.1, 95% CI 0.76–1.34) and CSS (HR 0.69, 95% CI 0.45–1.06) between EBRT plus BT compared to RP.

Conclusion: While cancer control affected by EBRT alone seems inferior to RP in patients with high-risk PCa, BT additive to EBRT was not different from RP. These data support the need for BT in addition to EBRT as part of multimodal RT for high-risk PCa.

Abbreviations: ADT: androgen-deprivation therapy; BT: brachytherapy; CSS: cancer-specific survival; HR: hazard ratio; MFS, metastatic-free survival; MOOSE: Meta-analyses of Observational Studies in Epidemiology; OR: odds ratio; OS: overall survival; PCa: prostate cancer; RR: relative risk; RP: radical prostatectomy; RCT: randomised controlled trials; (EB)RT: (external beam) radiation therapy

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Introduction

High-risk non-metastatic disease (i.e. PSA level >20 ng/mL, Gleason score of 8, and/or a clinical stage of T2c–3a) accounts for ~30% of newly diagnosed prostate cancer (PCa) [1,2], depending on its definition [3,4]. The optimal primary treatment for these patients

remains unresolved with standard local therapeutic options including radical prostatectomy (RP) and radiation therapy (RT) consisting of external beam RT (EBRT) with or without brachytherapy (BT). Owing to the heterogeneous nature of the published cohort studies

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This article has been corrected with minor changes. These changes do not impact the academic content of the article.

 Supplemental data for this article can be accessed [here](#).

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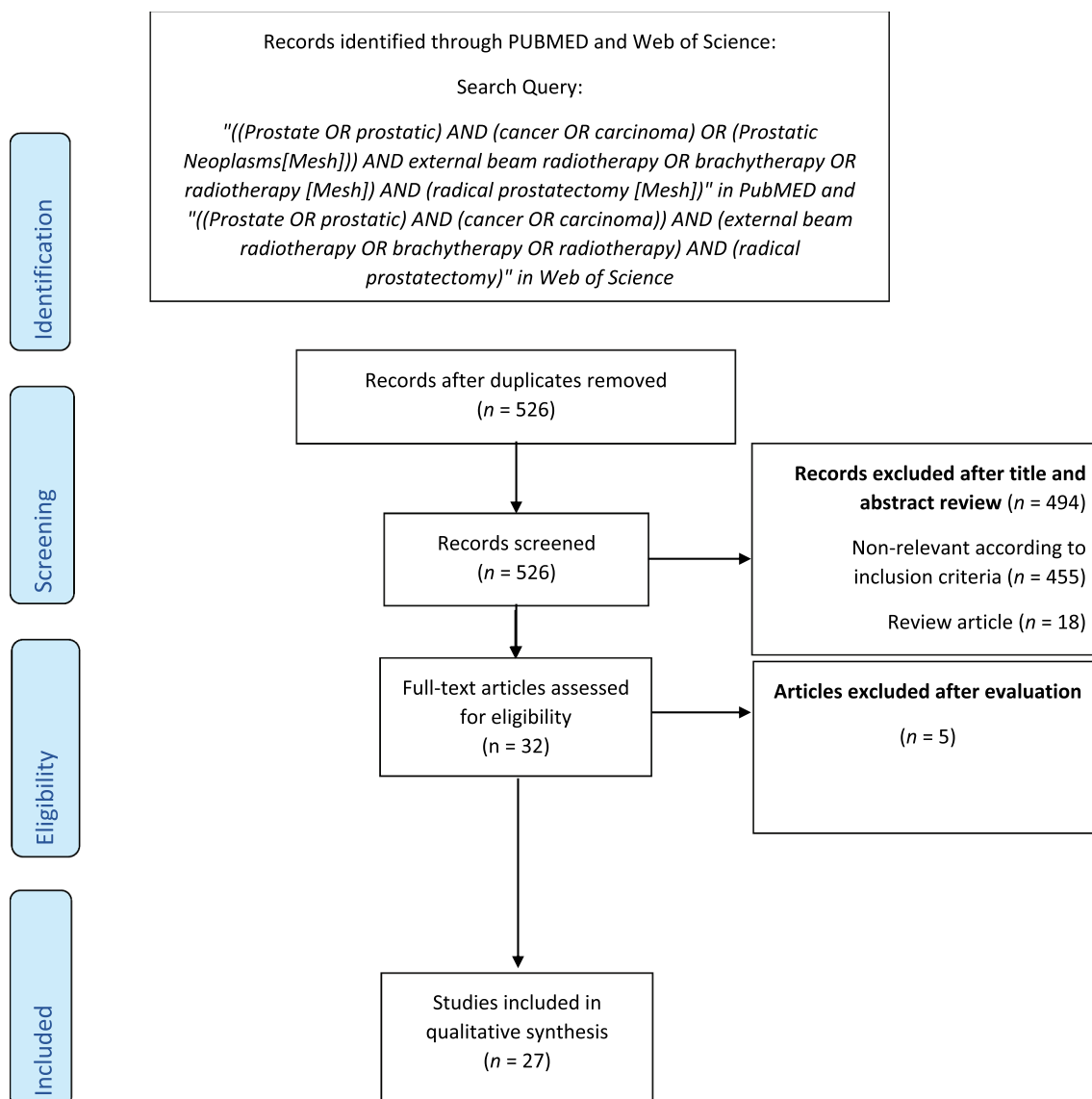


Figure 1. The selection process of the articles to assess survival outcomes among patients with high-risk prostate cancer who received RT compared to RP.

and the lack of prospective randomised controlled trials (RCTs), it remains unclear which single and/or multimodal therapeutic strategy is optimal for each patient with high-risk PCa.

In the current and likely future, the absence of propensity designed RCTs comparing RP to RT for patients with high-risk PCa, meta-analyses may help a framework for clinical decision-making and patient counselling. To this end, we performed a systematic review and meta-analysis to summarise the results of available studies including the latest literature on this subject. We focussed on the additive value of BT in addition to EBRT.

Methods

In this meta-analysis, we followed the Meta-analyses of Observational Studies in Epidemiology (MOOSE) statement guidelines that propose a checklist of items

which provides a RCTs checklist [5]. Moreover, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) was used.

Eligibility criteria

The question of this study was, 'Do patients with high-risk PCa who receive EBRT with or without BT have a better survival outcome compared to those who receive RP?'. All current articles covering the study question were eligible for this systematic review. We selected studies that perform quantitative synthesis according to the similarity in Population, Interest, Context (PICO) elements to decrease the selection bias and heterogeneity. The inclusion criteria for the quantitative meta-analysis were original research articles that assessed survival outcomes and reported an estimated risk effect (hazard ratio [HR], odds ratio [OR], relative risk [RR]) for both patient and control groups.

Exclusion criteria were BT usage alone as definitive therapy and lack of definition of high-risk PCa in the main or subgroup analysis.

Consequently, the more comparable cohort studies according to the MOOSE guidelines were included in the analyses. Furthermore, the heterogeneity of the population was explored by detecting the source and country of databases. According to OS, we categorised studies' outcomes, CSS, biochemical recurrence survival, and metastatic-free survival (MFS).

Information sources

We searched PubMed and the Web of Science for studies published before 1 January 2021. The search queries line and search strategies were '((Prostate OR prostatic) AND (cancer OR carcinoma) OR (Prostatic Neoplasms[Mesh])) AND external beam radiotherapy OR brachytherapy OR radiotherapy [Mesh]) AND (radical prostatectomy [Mesh])' in PubMed and '((Prostate OR prostatic) AND (cancer OR carcinoma)) AND (external beam radiotherapy OR brachytherapy OR radiotherapy) AND (radical prostatectomy)' in the Web of Science.

Table 1. Characteristics of the included studies of patients treated locally for high-risk prostate cancer.

Study	Year	High-risk PCa definition	Sample size, n	Intervention group	Control group	Outcomes	Radiation dose
Yasui et al. Japan (1970–2014) [8]	2020	T3	4810	EBRT	RP+ sRT	OS/CSS	NR
Zhou et al. [9]	2020	T3	9258	EBRT EBRT+BT	RP	OS/CSS	NR
Muralidhar et al. NCDB and SEER (2004–2012) [10]	2019	GS: 9–10	4367/ 2278	EBRT+BT	RP+aRT	OS	NR
Knipper et al. SEER 2004–2015 [11]	2019	GS: 9–10	16,018	EBRT	RP+aRT	OS/CSS	NR
Yin et al. SEER (2004–2015) [12]	2019	NCCN	62178	EBRT EBRT+BT	RP+aRT	OS/CSS	NR
Berg et al. NCDB (2004–2009) [13]	2019	NCCN	13985	EBRT+BT	RP	OS	NR
Jayadevappa et al. SEER–Medicare (1996–2003) [14]	2019	GS: ≥8 or T≥ T2c	4878	EBRT	RP	OS/CSS	NR
Reichard et al. MD Anderson (2004–2013); comparison with matched SEER cohort [15]	2019	NCCN	304	EBRT + BT	RP	OS/MFS	75.6 Gy
Ennis et al. NCDB (2004–2013) [16]	2018	NCCN	40123	EBRT EBRT+BT	RP	OS	NR
Tilki et al. Chicago Prostate Cancer Center, USA, and Martini-Klinik Prostate Cancer Center, Germany (1992–2013) [17]	2018	GS: 9–10	452	EBRT+BT	RP+aRT	CSS/OS	45 Gy IMRT + BT: ¹²⁵ I (108 Gy), ¹⁰³ Pa (90 Gy), ¹³¹ Cs (100 Gy)
Jang et al. SEER Medicare (1992–2009) [18]	2018	≥T3a or GS 8–10	7946	EBRT	RP+aRT	CSS/OS	NR
Kishan et al. University of California, Los Angeles (2000–2013) [19]	2018	NCCN	1373	EBRT EBRT+BT	RP	CSS/OS/ MFS	XRT: median 74.3 Gy XRT+BT: median 91.5 Gy
Robinson et al. NPCR of Sweden (1998–2012) [20]	2018	NCCN	41503	EBRT	RP	CSS	
Markovina et al. Washington University, St. Louis (2002–2011) [21]	2018	NCCN	124	EBRT	RP	OS/MFS	Median 75.6 Gy
Gu et al. SEER (2004–2008) [22]	2018	NCCN	7656	EBRT	RP	CSS/OS	NR
Feldman et al. SEER–Medicare (1992–2009) [23]	2017	T3	2935	EBRT	RP	OS/CSS	NR
Ciezki et al. Cleveland Clinic (1996–2012) [24]	2016	NCCN	2042	EBRT	RP	CSS/BRFS	78 Gy
Taguchi et al. University of Tokyo (2005–2012) [34]	2015	D'Amico	336	EBRT	RP	OS/CSS/ BRFS	Median 76 Gy
Yamamoto et al. Japan (1994–2005) [25]	2014	T3	231	EBRT	RP	OS/CSS	70 Gy (60–72)
Sooriakumaran et al. PCBaSe Sweden (1996–2010) [33]	2014	Modified NCCN	7649	EBRT	RP	CSS	NR
Merino et al. Pontificia Universidad Catolica de Chile (1999–2010) [26]	2013	D'Amico	294	EBRT	RP	CSS/BRFS	76 Gy
Hoffman et al. PCOS (1994–2010) [27]	2013	PSA >10 ng/mL or GS 8–10	437	EBRT	RP	OS/CSS	NR
Sun et al. SEER (1992–2005) [28]	2013	T2c	5945	EBRT	RP	OS/CSS	NR
Westover et al. 21st century oncology, Chicago Prostate Center, Duke University (1988–2008) [29]	2012	D'Amico	657	EBRT+BT	RP	CSS	45 Gy RT+ 90–108 Gy BT
Kibel et al. Barnes-Jewish Hospital and Cleveland Clinic (1995–2005) [30]	2012	D'Amico	1201	EBRT	RP	OS/CSS	Median 74 Gy (Barnes Jewish) and 78 Gy (Cleveland Clinic)
Abdollah et al. SEER (1992–2005) [31]	2012	T2c or GS 8–10	6057	EBRT	RP	OS/CSS	NR
Boorjian et al. MayoClinic, Fox Chase (1988–2004) [32]	2011	NCCN	1582	EBRT	RP	OS/CSS	72 Gy (50–79)

aRT: adjuvant RT; BRFS: biochemical recurrence-free survival; GS: Gleason score; IMRT: intensity modulated RT; NCDB: National Cancer Database; NCCN: National Comprehensive Cancer Network; NR: not reported; PCBaSe: Prostate Cancer data Base Sweden; PCOS: Prostate Cancer Outcomes Study; SEER: Surveillance, Epidemiology and End Results; sRT: salvage radiotherapy.

Table 2. The Newcastle-Ottawa scale for all studies in the quantitative synthesis.

Study	Selection	Comparability	Outcome	Total
Yasui et al. [8]	****	**	**	8
Zhou et al. [9]	****	**	**	8
Muralidhar et al. [10]	****	**	**	8
Knipper et al. [11]	****	**	***	9
Yin et al. [12]	****	**	**	8
Berg et al. [13]	****	**	**	8
Jayadevappa et al. [14]	****	**	**	8
Reichard et al. [15]	****	**	**	8
Ennis et al. [16]	****	**	*	7
Tilki et al. [17]	***	**	*	6
Jang et al. [18]	****	**	**	8
Kishan et al. [19]	****	**	*	7
Robinson et al. [20]	****	**	*	7
Markovina et al. [21]	****	**	*	7
Gu et al. [22]	****	**	**	8
Feldman et al. [23]	****	**	**	8
Ciecki et al. [24]	****	**	**	8
Taguchi et al. [34]	****	**	*	7
Yamamoto et al. [25]	****	**	**	8
Sooriakumaran et al. [33]	****	**	***	9
Merino et al. [26]	****	**	*	7
Hoffman et al. [27]	****	**	***	9
Sun et al. [28]	****	**	*	7
Westover et al. [29]	***	**	*	6
Kibel et al. [30]	****	**	**	8
Abdollah et al. [31]	****	**	**	8
Boorjian et al. [32]	***	**	**	7

*According to Newcastle-Ottawa scale, stars were awarded for each quality item such that highest quality studies were awarded up to 9 stars.

The search results were restricted to English language articles. Two reviewers screened titles and abstracts independently; any disagreement about the articles' eligibility was resolved by Delphi consensus with the co-authors. A data extraction sheet was developed based on the Cochrane Consumers and the Communication Review Group's (<http://ccrg.cochrane.org/author-resources>). We extracted the following data: first-author, type of article, year of publication, dates of the data collection or enrolment, cohort type, sample size, number of individuals on treatment, outcome, how the outcome was measured, type of effect statistic, effect statistic error measures, and effect statistic *P* value. There were no limitations in the articles' data, so we did not need to contact any authors for additional details. Modified Newcastle-Ottawa Scale criteria were used to assess the

quality of the included studies [6]. Subsequently, the HRs and 95% CIs with OS, CSS outcomes were retrieved, all discrepancies regarding data extraction were resolved by Delphi consensus with co-authors.

Statistical analysis

Forest plots were used to assess the multivariable HRs. We summarised them to depict the relationship of our outcomes with the type of treatment (i.e. RP, EBRT alone and EBRT plus BT). When HRs and *P* value only were reported, we calculated the corresponding 95% CIs. We utilised multivariable adjusted or propensity score matched analyses in the quantitative meta-analyses. Studies included in performing the meta-analyses were adjusted for the effects of age, clinical T stage, Gleason grade, and PSA. The primary meta-analysis was performed for all studies that reported OS as an outcome. A secondary meta-analysis was conducted using studies that reported CSS as an outcome. The next four meta-analyses were conducted among studies that reported the risk of OS and CSS according to the type of RT (i.e. EBRT alone or EBRT plus BT). Heterogeneity across the studies was appraised using *P* values, *Q* and *I*² statistics [7]. In the presence of statistically significant heterogeneity (>50%), random effect meta-analysis was used. When there was no significant heterogeneity observed, the fixed-effect model was used. Funnel plots was used to detect the risk of publication bias. Statistical analyses were considered significant if the *P* value was <0.05. All analyses were carried out using Stata version 14 (Stata Corp., College Station, TX, USA).

Results

After initial screening, 526 articles were available for assessment. The selection process for the systematic review is shown in Figure 1. With further assessment, according to inclusion and exclusion criteria, 27 studies were finally available for the systematic review and meta-analysis (Table 1) [8–34].

Table 3. Reported data regarding multimodal therapy among studies that used EBRT plus BT compared to RP.

Study	Adjuvant ADT, %		Adjuvant or salvage RT, %
	EBRT plus BT	RP	RP
Zhou et al. [9]	NR	NR	NR
Muralidhar et al. [10]	NR	NR	NR
Yin et al. [12]	NR	NR	NR
Berg et al. [13]	69	15	15
Jayadevappa et al. [14]	NR	NR	NR
Ennis et al. [16]	11.1	NR	NR
Tilki et al. [17]	1.0	8.8	15.7
Kishan et al. [19]	92.4	11.3	8.7
Westover et al. [29]	1.0	6	6

NR: not reported.

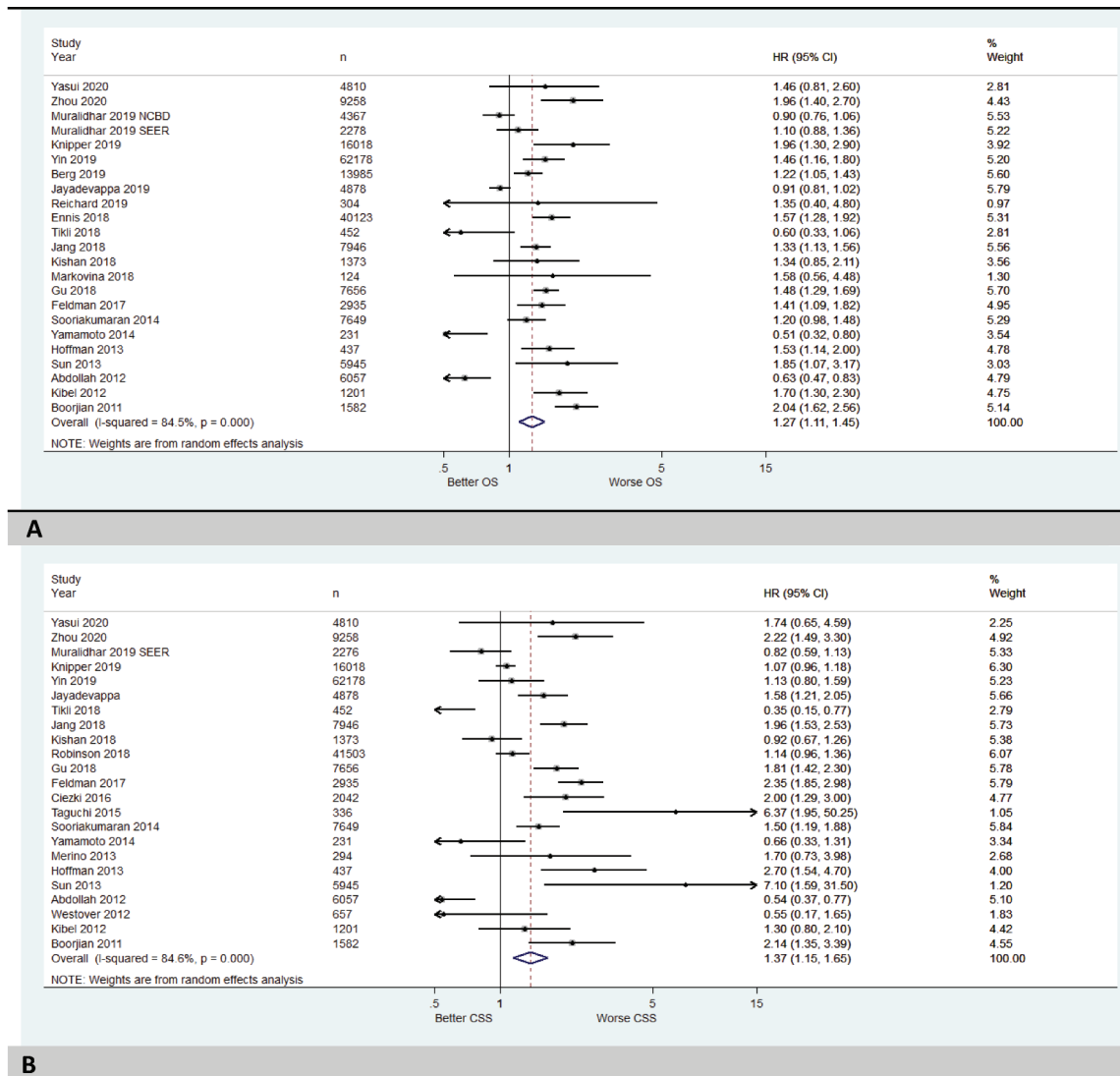


Figure 2. (a) Forest plots with summary HRs (all included study) for OS of the RT group vs RP (reference group) for high-risk prostate cancer. (b) Forest plots with summary HRs (all included study) for CSS of the RT group vs RP (reference group) for high-risk prostate cancer.

Almost all of the studies in this review were cohort studies. Of the 27 included studies, regardless of the type of RT (i.e. EBRT alone or EBRT plus BT), 23 studies assessed OS and CSS. The quality assessment of the included studies according to the Newcastle-Ottawa scale is summarised in Table 2 [8–34]. In general, there were only two fair quality studies, while all 25 others had at least good quality (Table 2).

OS and CSS for patients with high-risk PCa who received RT compared to RP

In the first meta-analysis of OS, 23 were included. We found that patients with high-risk PCa who received RT (regardless of the type of RT) had significantly worse OS than those treated with RP with a HR of 1.27 (95% CI 1.11–1.45; Figure 2(a)). The 23 studies included in the meta-analysis demonstrated a high heterogeneity ($I^2 = 84.5\%$,

$P < 0.001$), so a random-effect model was used. The funnel plot was asymmetrical (Figure 1S-A in supplemental data). In the second meta-analysis, 23 studies were again included. We found that patients with high-risk PCa who received RT (regardless of the type of RT) had significantly worse CSS than those treated with RP with a HR of 1.37 (95% CI 1.15–1.65; Figure 2(b)). The 23 studies included in the meta-analysis showed a high heterogeneity ($I^2 = 84.6\%$, $P < 0.001$), so a random-effect model was used. The funnel plot was asymmetrical (Figure 1S-B in supplemental data).

OS and CSS for patients with high-risk PCa who received only EBRT compared to RP

In the first subgroup meta-analysis, 15 studies were included. We found that patients with high-risk PCa who received EBRT alone (i.e. without

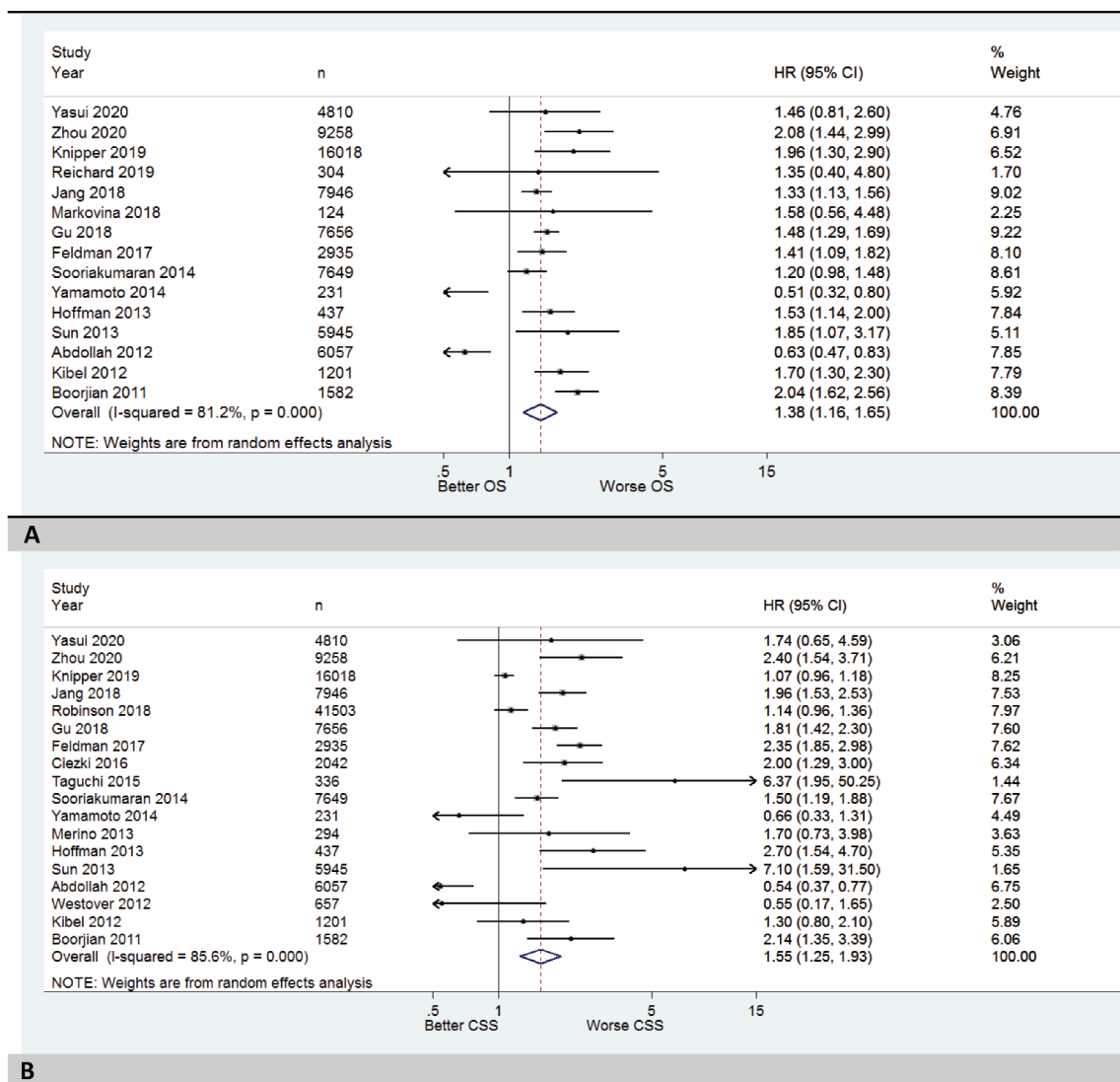


Figure 3. (a) Forest plots with summary HRs (only EBRT) for OS of the RT group vs RP (reference group) for high-risk prostate cancer. (b) Forest plots with summary HRs (only EBRT) for CSS of the RT group vs RP (reference group) for high-risk prostate cancer.

a concomitant BT) had significantly worse OS than those treated with RP with a HR of 1.38 (95% CI 1.16–1.65; [Figure 3\(a\)](#)). The 15 studies included in the meta-analysis demonstrated a high heterogeneity ($I^2 = 81.2\%$, $P < 0.001$), so a random-effect model was used. The funnel plot was slightly asymmetrical ([Figure 1S-C](#) in supplemental data). In the second subgroup meta-analysis, 18 studies were included. We found that patients with high-risk PCa who received EBRT alone had significantly worse CSS than those treated with RP with a HR of 1.55 (95% CI 1.25–1.93; [Figure 3\(b\)](#)). The 18 studies included in the meta-analysis showed a high heterogeneity ($I^2 = 85.6\%$, $P < 0.001$), so a random-effect model was used. The funnel plot was slightly asymmetrical ([Figure 1S-D](#) in supplemental data).

OS and CSS for patients with high-risk PCa who received EBRT plus BT compared to RP

In the third subgroup meta-analysis, eight studies were included. The HR of 1.1 (95% CI 0.76–1.34) suggested that there was no difference in OS between patients with high-risk PCa who received EBRT plus BT compared to those who underwent RP ([Figure 4\(a\)](#)). The eight studies included in the meta-analysis demonstrated a high heterogeneity ($I^2 = 92.8\%$, $P < 0.001$), so a random-effect model was used. The funnel plot was asymmetrical ([Figure 1S-E](#) in supplemental data). In the fourth subgroup meta-analysis, seven studies were included. The HR of 0.69 (95% CI 0.45–1.06) suggested no difference in CSS between patients with high-risk PCa who received EBRT plus BT and those who

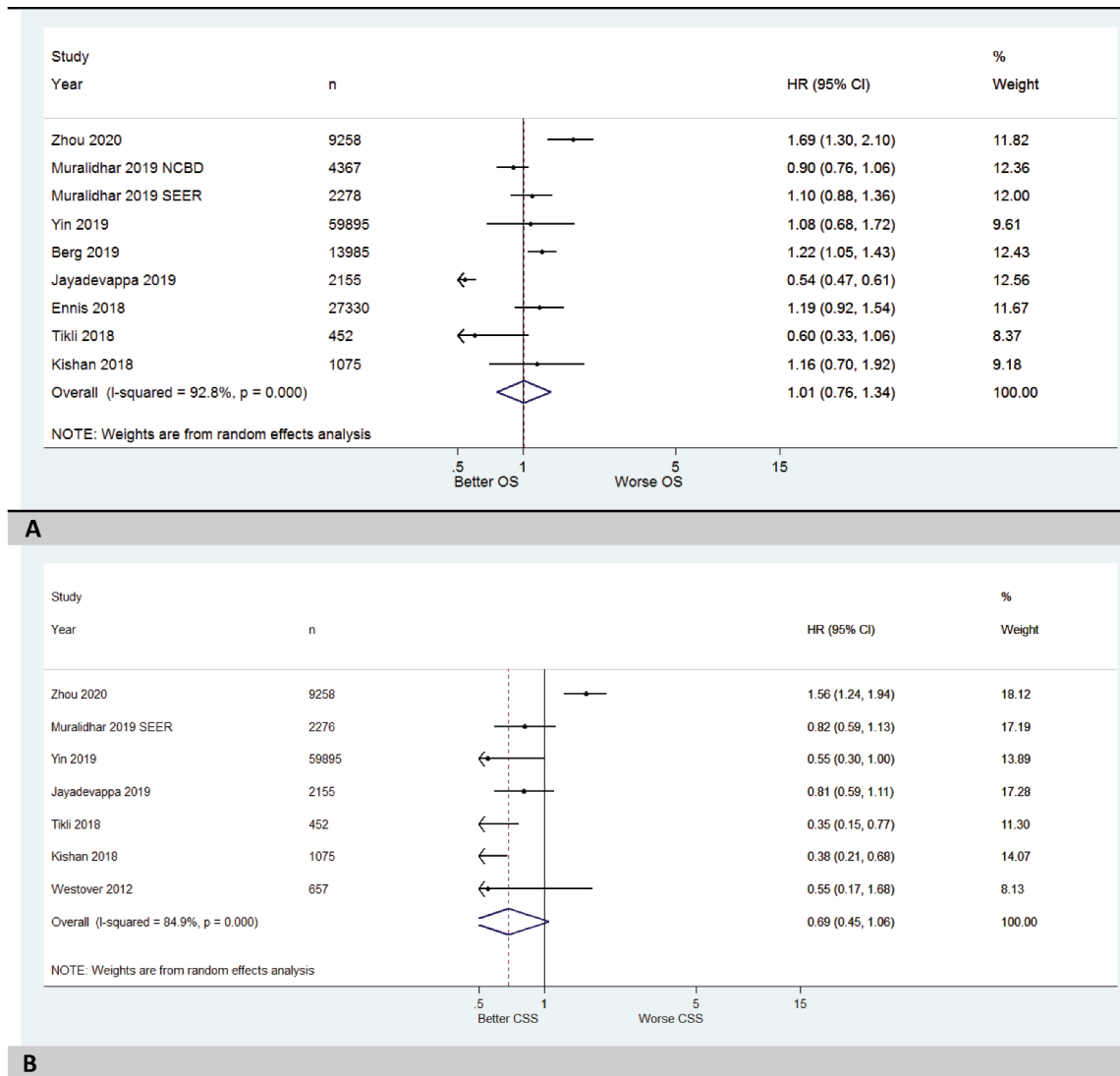


Figure 4. (a) Forest plots with summary HRs (EBRT plus BT) for OS of the RT group vs RP (reference group) for high-risk prostate cancer. (b) Forest plots with summary HRs (EBRT plus BT) for CSS of the RT group vs RP (reference group) for high-risk prostate cancer.

underwent RP; however, statistical significance was not reached (Figure 4(b)). The seven studies included in the meta-analysis showed moderate heterogeneity ($I^2 = 84.9\%$, $P = 0.096$), so a random-effect model was used. The funnel plot was slightly asymmetrical (Figure 1S-F in supplemental data). Table 3 [9,10,12–14,16,17,19,29] shows the reported data regarding RT and RP components among studies included in this systematic review.

Discussion

The present systematic review and meta-analyses assessed the comparative survival effectiveness of RT and RP as a definitive therapy with curative intent of PCa patients with high-risk features. Although we found that RT irrespective of RT type (i.e. EBRT alone or plus BT) resulted in significantly worse OS and CSS compared to RP, patients who underwent a EBRT plus

BT combination had OS and CSS that were not inferior to RP. However, EBRT alone (i.e. without concomitant BT) was inferior to RP with regards to OS and CSS.

While there is no direct, well designed comparison of RP vs RT as the first step in a multimodal therapeutic concept in concordance with our meta-analyses, cumulative data support the concept of combining maximal RT consisting of EBRT plus BT with androgen-deprivation therapy (ADT) as the first-line multimodal strategy for therapy of high-risk PCa [10,12,16,17,19,29]. Indeed, major guidelines recommend ADT combined with EBRT plus BT, based on the OS benefits shown in several RCTs that compared it to EBRT plus ADT [35]. There is to date no comparison between the different multimodal therapies (i.e. EBRT plus BT and ADT) vs RP with RT vs RP with ADT, etc. Some single institution and small cohorts included in this systematic review tried to conduct a fair comparison between those strategies (i.e. RP plus adjuvant/salvage RT and ADT) [17,19,36,37]; however, the

inherent selection bias limits any fair comparisons (Table 2), this is especially true for in multi-institutional and population-based datasets and registries, while they are at least likely to suffer from systematic bias based on their geographic and specialty representativeness.

Today, RT as adjuvant or salvage strategy is supported as a part of a multimodal therapy after RP by major guidelines for patients with high-risk PCa based on data recruiting from several RCTs [38–40]. However, more studies that compared EBRT plus BT to RP have not reported postoperative RT usage, therefore making fair comparisons impossible [9,10,12,14,16]. Limitations for optionally combining BT with EBRT include dose distribution and prostate size, reflecting a selection bias that may reflect the local tumour burden. In contrast to most cohort studies that assessed EBRT (i.e. without a concomitant BT) vs RP for high-risk disease, we found a significantly worse OS and CSS [9,11,18,22]. Finally, until well-designed RCTs assess survival outcomes between MaxRT and MaxRP, a multidisciplinary approach should be considered in treating patients with high-risk PCa beyond the results of survival outcomes of cohort studies.

The main limitation of the present systematic review and meta-analysis was the lack of well-designed controlled trials. However, because of this lack, we believe that this systematic review and meta-analysis might help frame and equipoise decisions to guide patients' counselling as part of the shared decision process [5]. Another limitation was the heterogeneity across studies regarding the age of included patients, usage of ADT and its ADT duration, usage of adjuvant or salvage therapies such as postoperative RT after RP. Moreover, there was no precise data regarding the number of ADT patients, making subgroup analysis impossible. Indeed, designing a cohort study considering and adjusting for all variables' effects is unlikely to be possible/to be performed. On the other hand, it is clear that the included multi-institutional cohorts suffer from a significant selection bias that limits the validity of the findings assessing from the former. Moreover, the effect of delayed definitive therapy due to the coronavirus disease 2019 (COVID-19) pandemic should be considered in future studies [41,42].

Conclusions

According to this systematic review and meta-analyses, patients with high-risk PCa who received EBRT alone (without a concomitant BT) as a first-line definitive therapy had worse OS and CSS than those who underwent RP. However, EBRT plus BT as a multimodal RT was not inferior to RP in high-risk PCa. These data support the need for a multimodal strategy to achieve optimal therapy in high-risk PCa.

RT as a primary definitive strategy could be better when combined with EBRT and BT to achieve maximal radiation dose combined with ADT. The role, timing, indication of postoperative RT after RP, and the type and duration of ADT for each patient need assessment and evidence. Until then, we would postulate based on the findings of our present study an equipoise of EBRT with BT for local control as a part of multimodal flexible and dynamic treatment strategy tailored to each tumour in each patient.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

References

- [1] Lughezzani G, Briganti A, Karakiewicz PI, et al. Predictive and prognostic models in radical prostatectomy candidates: a critical analysis of the literature. *Eur Urol* 2010 [accessed 2021 Jan 9];58:687–700. Available from: <http://www.sciencedirect.com/science/article/pii/S0302283810006974>.
- [2] Gallina A, Chun FK, Suardi N, et al. Comparison of stage migration patterns between Europe and the USA: an analysis of 11 350 men treated with radical prostatectomy for prostate cancer. *BJU Int*. 2008;101:1513–1518.
- [3] Cooperberg MR, Cowan J, Broering JM, et al. High-risk prostate cancer in the United States, 1990–2007. *World J Urol*. 2008;26:211–218.
- [4] Shariat SF, Kattan MW, Vickers AJ, et al. Critical review of prostate cancer predictive tools. *Future Oncol*. 2009;5:1555–1584.
- [5] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA*. 2000;283:2008–2012.
- [6] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25:603–605.

- [7] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
- [8] Yasui M, Sakaguchi M, Jikuya R, et al. Comparative effectiveness of surgery and radiotherapy for survival of patients with clinically localized prostate cancer: a population-based coarsened exact matching retrospective cohort study. *Oncol Lett*. 2020;20:150.
- [9] Zhou X, Jin K, Qiu S, et al. Comparing effectiveness of radical prostatectomy versus external beam radiotherapy in patients with locally advanced prostate cancer. *Medicine (Baltimore)*. 2020;99(34):e21642.
- [10] Muralidhar V, Mahal BA, Butler S, et al. Combined external beam radiation therapy and brachytherapy versus radical prostatectomy with adjuvant radiation therapy for Gleason 9-10 prostate cancer. *J Urol*. 2019;202:973–978.
- [11] Knipper S, Palumbo C, Pecoraro A, et al. Survival outcomes of radical prostatectomy vs. external beam radiation therapy in prostate cancer patients with Gleason Score 9-10 at biopsy: a population-based analysis. *Urol Oncol*. 2020;38:79.e9–79.e14.
- [12] Yin M, Zhao J, Monk P, et al. Comparative effectiveness of surgery versus external beam radiation with/without brachytherapy in high-risk localized prostate cancer. *Cancer Med*. 2020;9:27–34.
- [13] Berg S, Cole AP, Krimphove MJ, et al. Comparative effectiveness of radical prostatectomy versus external beam radiation therapy plus brachytherapy in patients with high-risk localized prostate cancer. *Eur Urol*. 2019;75:552–555.
- [14] Jayadevappa R, Lee DI, Chhatre S, et al. Comparative effectiveness of treatments for high-risk prostate cancer patients. *J Urol Oncol*. 2019;37:574.e11–574.e18.
- [15] Reichard CA, Hoffman KE, Tang C, et al. Radical prostatectomy or radiotherapy for high- and very high-risk prostate cancer: a multidisciplinary prostate cancer clinic experience of patients eligible for either treatment. *BJU Int*. 2019;124:811–819.
- [16] Ennis RD, Hu L, Ryemon SN, et al. Brachytherapy-based radiotherapy and radical prostatectomy are associated with similar survival in high-risk localized prostate cancer. *J Clin Oncol*. 2018;36:1192–1198.
- [17] Tilki D, Chen MH, Wu J, et al. Surgery vs radiotherapy in the management of biopsy Gleason score 9-10 prostate cancer and the risk of mortality. *JAMA Oncol*. 2019;5:213–220.
- [18] Jang TL, Patel N, Faiena I, et al. Comparative effectiveness of radical prostatectomy with adjuvant radiotherapy versus radiotherapy plus androgen deprivation therapy for men with advanced prostate cancer. *Cancer*. 2018;124:4010–4022.
- [19] Kishan AU, Cook RR, Ciezki JP, et al. Radical prostatectomy, external beam radiotherapy, or external beam radiotherapy with brachytherapy boost and disease progression and mortality in patients with Gleason score 9-10 prostate cancer. *JAMA*. 2018;319:896–905.
- [20] Robinson D, Garmo H, Lissbrant IF, et al. Prostate cancer death after radiotherapy or radical prostatectomy: a nationwide population-based observational study. *Eur Urol*. 2018;73:502–511.
- [21] Markovina S, Meeks MW, Badiyan S, et al. Superior metastasis-free survival for patients with high-risk prostate cancer treated with definitive radiation therapy compared to radical prostatectomy: a propensity score-matched analysis. *Adv Radiat Oncol*. 2018;3:190–196.
- [22] Gu X, Gao X, Cui M, et al. Survival outcomes of radical prostatectomy and external beam radiotherapy in clinically localized high-risk prostate cancer: a population-based, propensity score matched study. *Cancer Manag Res*. 2018;10:1061–1067.
- [23] Feldman AS, Meyer CP, Sanchez A, et al. Morbidity and mortality of locally advanced prostate cancer: a population based analysis comparing radical prostatectomy versus external beam radiation. *J Urol*. 2017;198:1061–1068.
- [24] Ciezki JP, Weller M, Reddy CA, et al. A comparison between low-dose-rate brachytherapy with or without androgen deprivation, external beam radiation therapy with or without androgen deprivation, and radical prostatectomy with or without adjuvant or salvage radiation therapy for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2017;97:962–975.
- [25] Yamamoto S, Masuda H, Urakami S, et al. Patient-perceived satisfaction after definitive treatment for men with high-risk prostate cancer: radical prostatectomy vs. intensity-modulated radiotherapy with androgen deprivation therapy. *Urology*. 2015;85:407–413.
- [26] Merino T, San Francisco IF, Rojas PA, et al. Intensity-modulated radiotherapy versus radical prostatectomy in patients with localized prostate cancer: long-term follow-up. *BMC Cancer*. 2013;13:530.
- [27] Hoffman RM, Koyama T, Fan KH, et al. Mortality after radical prostatectomy or external beam radiotherapy for localized prostate cancer. *J Natl Cancer Inst*. 2013;105:711–718.
- [28] Sun M, Sammon JD, Becker A, et al. Radical prostatectomy vs radiotherapy vs observation among older patients with clinically localized prostate cancer: a comparative effectiveness evaluation. *BJU Int*. 2014;113:200–208.
- [29] Westover K, Chen M-H, Moul J, et al. Radical prostatectomy vs radiation therapy and androgen-suppression therapy in high-risk prostate cancer. *BJU Int*. 2012;110:1116–1121.
- [30] Kibel AS, Ciezki JP, Klein EA, et al. Survival among men with clinically localized prostate cancer treated with radical prostatectomy or radiation therapy in the prostate specific antigen era. *J Urol*. 2012;187:1259–1265.
- [31] Abdollah F, Schmitges J, Sun M, et al. Comparison of mortality outcomes after radical prostatectomy versus radiotherapy in patients with localized prostate cancer: a population-based analysis. *Int J Urol*. 2012;19:836–844.
- [32] Boorjian SA, Karnes RJ, Viterbo R, et al. Long-term survival after radical prostatectomy versus external-beam radiotherapy for patients with high-risk prostate cancer. *Cancer*. 2011;117:2883–2891.
- [33] Sooriakumaran P, Nyberg T, Akre O, et al. Comparative effectiveness of radical prostatectomy and radiotherapy in prostate cancer: observational study of mortality outcomes. *BMJ*. 2014;348:g1502.
- [34] Taguchi S, Fukuhara H, Shiraishi K, et al. Radical prostatectomy versus external beam radiotherapy for cT1-4N0M0 prostate cancer: comparison of patient outcomes including mortality. *PLoS One*. 2015;10:e0141123.

- [35] Mottet N, Cornford P, van den Bergh RC, et al. EAU guidelines: prostate cancer; 2020. [cited 2020 Dec 25]. Available from: <https://uroweb.org/guideline/prostate-cancer/>.
- [36] Motlagh RS, Abufaraj M, Mori K, et al. The efficacy and safety of relugolix compared with degarelix in advanced prostate cancer patients: a network meta-analysis of randomized trials. *Eur Urol Oncol*. 2021. Online ahead of print. DOI:10.1016/j.euo.2021.07.002.
- [37] Dearnaley DP, Saltzstein DR, Sylvester JE, et al. The oral gonadotropin-releasing hormone receptor antagonist relugolix as neoadjuvant/adjuvant androgen deprivation therapy to external beam radiotherapy in patients with localised intermediate-risk prostate cancer: a randomised, open-label, parallel-group phase 2 trial. *Eur Urol*. 2020;78:184–192.
- [38] Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet*. 2012;380:2018–2027.
- [39] Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol*. 2009;27:2924–2930.
- [40] Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol*. 2009;181:956–962.
- [41] Laukhtina E, Sari Motlagh R, Mori K, et al. Oncologic impact of delaying radical prostatectomy in men with intermediate- and high-risk prostate cancer: a systematic review. *World J Urol*. 2021;39(11):4085–4099.
- [42] Sari MR, Abufaraj M, Karakiewicz PI, et al. Association between SARS-CoV-2 infection and disease severity among prostate cancer patients on androgen deprivation therapy: a systematic review and meta-analysis. *World J Urol*. 2021. Online ahead of print. DOI:10.1007/s00345-021-03810-6.