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Scientific Article

A Novel Salvage Option for Local Failure in Prostate Cancer, Reirradiation Using External Beam or Stereotactic Radiation Therapy: Systematic Review and Meta-Analysis

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Abstract

Purpose: Reirradiation (re-RT) using external beam radiation therapy (EBRT) is a novel salvage strategy for local failure in prostate cancer. We performed a systematic review describing oncologic and toxicity outcomes for salvage EBRT/stereotactic radiation therapy (SBRT) re-RT.

Methods and Materials: A International Prospective Register of Systematic Reviews registered (#141466) systematic review, meta-analysis, and meta-regression was conducted using preferred reporting items for systematic reviews and meta-analyses guidelines. PubMed and EMBASE were searched from inception through September 2019. Outcome measures included local control (LC), biochemical relapse free survival (BRFS), and ≥grade 3 genitourinary (GU)/gastrointestinal (GI) toxicity. EBRT and SBRT data were collected separately. Meta-regression explored disease and toxicity outcomes as a function of equivalent dose in 2 Gy fractions (EQD2), length of follow-up, and partial versus whole prostate reirradiation.

Results: Nineteen studies representing 13 cohorts were included (428 patients). Weighted mean follow-up was 26.1 months. Median re-RT EQD2 was 77.1 Gy ($\alpha/\beta = 1.5$), with 92% of patients receiving SBRT, 52.1% of patients receiving partial prostate re-RT, and 30.1% of patients receiving androgen deprivation therapy with re-RT. LC was 83.2% (95% confidence interval [CI], 75.5%-90.9%) and BRFS was 59.3% (47.9%-70.7%). Reported late toxicity ≥grade 3 was 3.4% (95% CI, 1.0%-5.8%) for GU and 2.0% (95% CI, 0.1%-4.0%) for GI. Meta-regression found higher LC, BRFS, and reported GU/GI toxicity with increasing EQD2, with partial prostate re-RT associated with less reported GU/GI toxicity and no detriment to LC and BRFS.

Conclusions: Salvage re-RT using EBRT, particularly with SBRT, is an emerging technique to treat isolated local failure of prostate cancer. With short-term follow-up, LC, BRFS, and reported toxicities appear reasonable, although further follow-up is required before definitive statements on late toxicities can be made. Our review is limited by incomplete reporting of androgen deprivation therapy use in the primary literature. Further prospective studies and longer follow-up are needed before considering re-RT as standard practice.

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Introduction

Patients with newly diagnosed prostate cancer have numerous treatment options available to them. For those choosing external beam radiation therapy (EBRT),

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although dose escalation has resulted in improved biochemical control,[1,2] the most common first site of recurrence is still locally in the prostate.[3] Androgen deprivation therapy (ADT) is often the treatment of choice at biochemical recurrence, but is a noncurative treatment associated with a detriment to quality of life due to a wide range of side effects.[4] Castrate resistance occurs after a median time of approximately 18 to 36 months,[5,6] requiring many men to undergo further lines of systemic therapy for what may have first been an isolated local recurrence, with potential cure using local salvage therapy.

Traditional local salvage options after radiation therapy (RT) failure have included radical prostatectomy (RP), brachytherapy, cryotherapy, and high-intensity focused ultrasound (HIFU), which are endorsed per National Comprehensive Cancer Network guidelines.[7] Salvage RP has the longest history of use, with 5-year biochemical relapse free survival (BRFS) results ranging from 47% to 82%,[8] albeit with 41% of men suffering from varying degrees of incontinence, 24% having bladder neck strictures, and up to a 5% rectal injury rate.[9-11] Brachytherapy, cryotherapy, and HIFU are possibly less invasive salvage options with similar disease control rates, but are still associated with potentially serious toxicity.[12-14] Given the potential toxicity, variable outcomes, and limited access to these specialized salvage techniques, fewer than 2% of eligible patients undergo local salvage.[15]

A longstanding principle in radiation oncology is that after definitive EBRT has been delivered, reirradiation (re-RT) will exceed normal tissue tolerances, leading to concerns of futility or potentially serious toxicity.[16] However, new imaging and RT platforms have been developed that could allow for safer re-RT. Re-RT with palliative intent is safe and effective in bone[17] and brain[18] metastases, and in carefully selected patients, is feasible with radical intent in previously radiated lung,[19] breast,[20] and head and neck cancers.[21] Re-RT may also be less invasive, not requiring a general anesthetic or hospital admission, and it is more generalizable given the wide availability of image-guided RT platforms. In this context, our objective was to systematically review the literature for studies reporting outcomes or toxicity of re-RT for local failure of prostate cancer using EBRT or stereotactic radiation therapy (SBRT) after previous RT.

Methods and Materials

Search strategy

We conducted a International Prospective Register of Systematic Reviews registered (#141466), preferred reporting items for systematic reviews and meta-analyses based[22] systematic literature search of the PubMed and EMBASE databases from inception to September 6, 2019. Our search strategy is available in Appendix E1 and included keywords such as *prostate cancer, external beam radiotherapy, salvage radiotherapy, stereotactic radiotherapy,* and *reirradiation*.

Inclusion/exclusion criteria

English studies that reported oncologic or toxicity data of prostate re-RT using EBRT/SBRT were included. Re-RT after RP and prostate bed RT were both eligible and data were recorded separately where possible. Records were screened by title, then by abstract. Article review was conducted by 2 authors to confirm full-text eligibility. Reference lists of included studies were reviewed to identify additional studies. Studies using brachytherapy without EBRT/SBRT, palliative re-RT, or re-RT for a primary tumor other than prostate cancer were excluded. Reviews, case reports, and case series with fewer than 5 patients were excluded. To avoid duplication of study results, the most recently published data were included when duplicate study cohorts were encountered and $>33\%$ of the previous study cohort was included in a subsequent study.

Data abstraction

Data abstraction was performed with a standardized collection form by 2 study authors, with disagreements resolved through consensus and involvement of a third study author if necessary. The data collection form is available upon request. We used the definition of local control (LC) and BRFS as reported in each study. Data for EBRT/SBRT were recorded separately. SBRT was defined as per the description within each study, or RT using a limited number of fractions of ≥ 5 Gy per fraction. Partial prostate re-RT was defined as any RT omitting some component of the prostate from the clinical target volume (CTV) and included focal re-RT and hemiprostate re-RT. Whole prostate re-RT included patients who received a simultaneous in-field boost in addition to whole prostate re-RT.

Statistical methods

The primary outcome was LC at the last follow-up as defined by each study. Secondary outcomes included BRFS, distant metastasis free survival, overall survival, and Common Terminology Criteria for Adverse Events genitourinary (GU) and gastrointestinal (GI) acute and late toxicity. Definitions of LC and BRFS were rarely explicitly reported. If actuarial outcomes were reported and discordant with outcomes at the last follow-up, the worse outcome was selected (ie, lower LC, BRFS; higher rate of GU/GI toxicity). When studies did not report outcomes separately (ie, whole vs partial prostate re-RT),

the most commonly used feature was used for subgroup analysis.

Statistical analyses were performed using OpenMeta [Analyst].[23] A random effects meta-analysis of proportions using the Dersimonian and Laird method was used.[24] A correction factor of 0.5 was used when an event rate was 0%. Heterogeneity was assessed using the Cochran Q test and the I^2 statistic and considered significant when I^2 was >50% and the *P* value of the Q test was <0.10. The effect of re-RT equivalent dose in 2 Gy fractions (EQD2, $\alpha/\beta = 1.5$), length of study follow-up in months, and partial versus whole prostate re-RT on LC, BRFS, and GU/GI late toxicity ≥grade 3 were evaluated using multivariate meta-regression using a random effects model.[25] We conducted a subgroup analysis of studies that used SBRT using our meta-regression.

Results

Study characteristics

Our search strategy and supplemental literature search revealed 2658 records (Fig 1). Nineteen full text publications met our eligibility criteria, representing 13 patient data cohorts with 428 patients.[26-38] Nineteen studies were included in the qualitative portion of our systematic review, and the 13 separate patient data cohorts were included when reporting oncologic outcomes, toxicity, and the quantitative meta-analysis. Only 1 study was prospective,[27] and the remainder were retrospective. Of the 6 articles meeting eligibility criteria but not included in the quantitative analysis, 5 studies contained a major amount of overlap with a larger and more recently published study population,[39-43] and 1 study further detailed toxicity of re-RT[44] of an otherwise included study.[28]

Patient demographics, treatment details, toxicity, and oncologic outcomes are summarized in Table 1. The weighted median follow-up of included studies was 26.1 months, with a range from 11.7 to 94 months. The median interval between initial RT and re-RT ranged from 4.1 to 8.4 years. The median initial RT dose was 74 Gy. The weighted median prostate-specific antigen (PSA) at re-RT was 3.75 ng/mL.

Four studies mandated a positive biopsy for entry, with the remainder diagnosing local recurrence with a

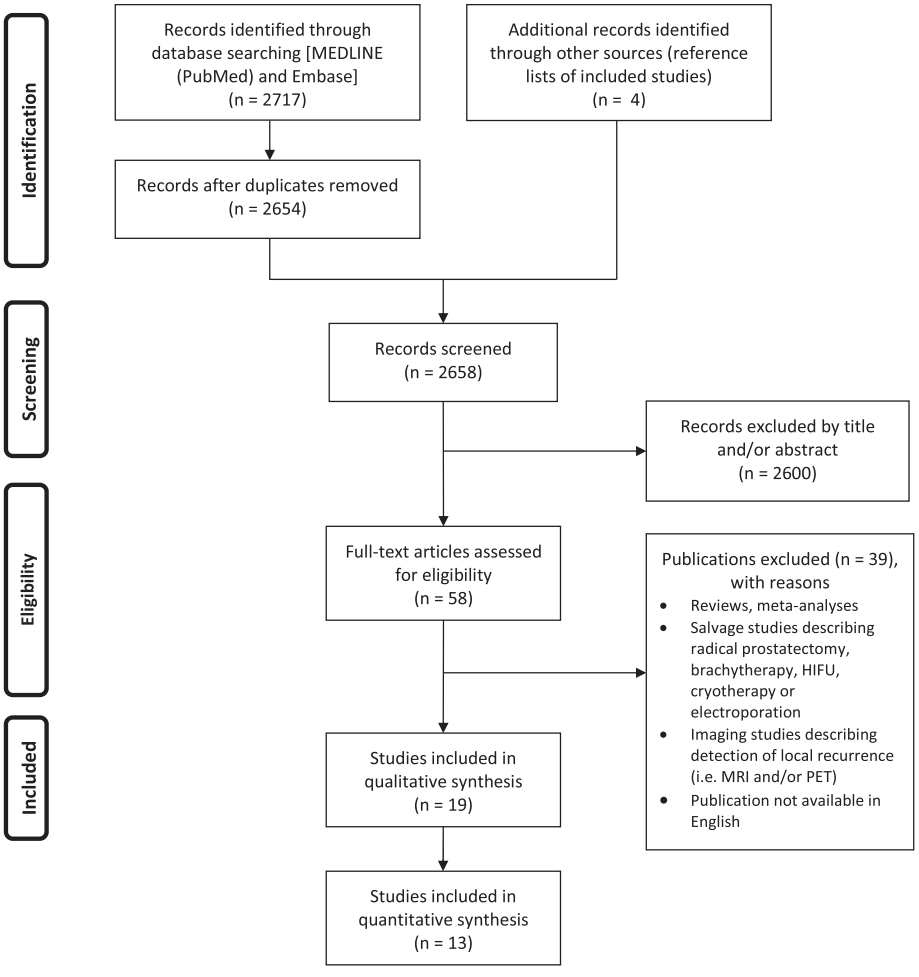

Figure 1 Preferred reporting items for systematic reviews and meta-analyses diagram of study selection for our systematic review.

Table 1 Summary table of studies reporting re-RT for prostate cancer

First author, country	No. Pts	Follow -up, median	Age at re-RT, years	Previous treatment(s) (median dose, range)	PSA at re-RT (median, range)	Duration between RT and re-RT (median, range)	How was LR defined	PET before re-RT
Kaplan[26] USA	6	16.5 mo	NR	I-125 BT (dose NR)	NR	52.5 mo (24-72 mo)	Biopsy	0/6
Fuller[27] USA	29	24 mo	Median 73	EBRT (27/29): 73.8 Gy (68.4-81 Gy), other: SBRT, I-125 BT	3.1 (0.1-48.6)	88 mo (32-200 mo)	Biopsy	0/29
Zilli[28] Switzerland	14	94 mo	Median 68	EBRT (12/14) EBRT + BT (2/14): 74 Gy (66-98.4 Gy)	7.4 (3.3-27.4)	73.2 mo (56.4-122.4 mo)	Biopsy, PET and/or MRI	11/14 (78.6%) ^{18}F-choline or ^{11}C-acetate
Janoray[29] France	21	11.7 mo	Mean 74.6	RP + EBRT (10/21): 70 Gy (45-76 Gy) EBRT (11/21): 72 Gy (70-76.5 Gy)	RP + EBRT: 3 (0.42-14.5) EBRT: 3.43 (1.65-24.1)	98 mo (37.9-398 mo)	PET and MRI	17/21 (81.0%) ^{18}F-choline
Rutenberg[30] USA	11	26.5 mo	Median 67	BT (144-145 Gy)	4.7 (3.6-15.3)	49.2 mo (12.9-135.5 mo)	Biopsy	0/11
Mbeutcha[31] France	18	14.5 mo	Median 69	BT (15/18) EBRT (3/18) (dose NR)	4.5 (IQR: 3.0-6.3)	77 mo (IQR: 64-92 mo)	Biopsy, PET and/or MRI	18/18 (100%) ^{11}C-acetate
Loi[32] Italy	50	21.3 mo	Median 76	EBRT (28/50), RP + EBRT (22/50): 74 Gy (60-80 Gy)	2.6 (1-30)	76 mo (9-205 mo)	PET and MRI	50/50 (100%) ^{18}F-choline
Miszczyk[33] Poland	38	14.4 mo	Median 71.6	EBRT (30/38), other: BT, EBRT + BT, RP + EBRT, RP + EBRT + BT: 76 Gy (45-138 Gy)	4.3 (0.44-66)	101 (22-179 mo)	Biopsy, PET and/or MRI	12/38 (31.6%) ^{18}F-choline or PSMA
Jereczek-Fossa[34] Italy	64	26.1 mo	Median 73.2	EBRT (40/64), RP + EBRT (19/64), other: EBRT + BT, BT: 70.2 Gy (45-145 Gy)	3.89 (0.17-51.8)	99.7 mo (23-208.4 mo)	Biopsy, PET and/or MRI	53/64 (82.8%) ^{11}C-choline
D'Agostino[35] Italy	23	33 mo	Median 78	RP + EBRT (8/23), EBRT (15/23): 74 Gy (66-76 Gy)	3.2 (1.2-13.5)	90 mo (26-138 mo)	PET	23/23 (100%) ^{11}C-choline
Olivier[36] France	12	34.2 mo	Median 58	RP + EBRT: 66 Gy (66-72 Gy)	1.13 (0.57-5.71)	77.5 mo (21-161 mo)	Biopsy, PET and/or MRI	12/12 (100%) ^{11}C-choline or PSMA

Pasquier[37] France/ Italy	100	29.3 mo	Median 71.2	EBRT: 74 Gy (66.6-80 Gy)	4.3 (2.0-38.3)	90 mo (24-216 mo)	Biopsy	94/100 (94%) Choline (not specified)
Scher[38] France	42	21 mo	Median 64	EBRT (33/32): 74 Gy (70-76 Gy), RP + EBRT (9/42): 68 Gy (65-70 Gy)	3.1 (0.01-23.7)	82.5 mo (29-207 mo)	Biopsy, PET and/or MRI	42/42 (100%) Choline (not specified)

Partial versus whole prostate re-RT	Treatment delivery	Most common re-RT dose (EQD2 range, $\alpha/\beta = 1.5$)	Acute GU toxicity	Acute GI toxicity	Late GU toxicity	Late GI toxicity	LC	BRFS	OS
Whole	EBRT system, delivery NR	60 Gy/30 fx, 1 month break after 15 fx, 4/6 concurrent hyperthermia	Gr 1: 0% Gr 2: 0% Gr 3: 0% Gr 4: 0%	Gr 1: 16.7% Gr 2: 0% Gr 3: 0% Gr 4: 0%	Gr 1: 0% Gr 2: 0% Gr 3: 0% Gr 4: 0%	Gr 1: 16.7% Gr 2: 0% Gr 3: 0% Gr 4: 0%	66.7%	NR	66.7%
Whole	Cyberknife timing NR	34 Gy/5 fx [80.6 $Gy_{1.5}$]	Gr 1: NR Gr 2: 0% Gr 3: 3.5% Gr 4: 0%	Gr 1: NR Gr 2: 0% Gr 3: 0% Gr 4: 0%	Gr 1: NR Gr 2: 10.3% Gr 3: 3.5% Gr 4: 3.5%	Gr 1: NR Gr 2: 0% Gr 3: 0% Gr 4: 0%	100%	82%	100%
Whole	10/14 3D-CRT, 4/14 IMRT 10/14 BT boost	Standard fractionation, 10/14 BT boost. 85 $Gy_{1.5}$ [70 - 93.4 $Gy_{1.5}$]	Gr 1: 14.3% Gr 2: 71.4% Gr 3: 0% Gr 4: 0%	Gr 1: 42.9% Gr 2: 14.3% Gr 3: 0% Gr 4: 0%	Gr 1: 21.4% Gr 2: 21.4% Gr 3: 29% Gr 4: 29%	Gr 1: 7.1% Gr 2: 21.4% Gr 3:28.6% Gr 4:36%	42.9%	28.6%	76%
Partial	Cyberknife treatment EOD	36.25 Gy/5 fx (15/21) [77.1 − 90.6 $Gy_{1.5}$]	Gr 1: 14.3% Gr 2: 4.8% Gr 3: 0% Gr 4: 0%	Gr 1: 9.5% Gr 2: 0% Gr 3: 0% Gr 4: 0%	Gr 1: 4.8% Gr 2: 0% Gr 3: 0% Gr 4: 0%	Gr 1: 0% Gr 2: 0% Gr 3: 0% Gr 4: 0%	90.6%	85.7%	NR
Whole	EBRT system, delivery NR	Standard fractionation, median 70.2 Gy, [64.8 - 75.6 Gy]	Gr 1: 54.6% Gr 2: 9.1% Gr 3: 0% Gr 4: 0%	Gr 1: 27.3% Gr 2: 9.1% Gr 3: 0% Gr 4: 0%	Gr 1: 9.1% Gr 2: 18.2% Gr 3: 18.2% Gr 4: 0%	Gr 1: 18.2% Gr 2: 9.1% Gr 3: 9.1% Gr 4:0%	NR	63.6%	77%
Partial	Cyberknife treatment daily	35 Gy/5 fx [85 $Gy_{1.5}$]	Gr 1: 55.6% Gr 2: 22.2% Gr 3: 0% Gr 4: 0%	Gr 1: 12.5% Gr 2: 25% Gr 3: 0% Gr 4: 0%	Gr 1: 33.3% Gr 2: 8.3% Gr 3: 5.6% Gr 4: 0%	Gr 1: 0% Gr 2: 10% Gr 3: 0% Gr 4: 0%	NR	55.6%	NR
Partial	Cyberknife treatment EOD	35 Gy/5 fx [85 $Gy_{1.5}$]	Gr 1: 18% Gr 2: 2% Gr 3: 2% Gr 4: 0%	Gr 1: 8% Gr 2: 0% Gr 3: 0% Gr 4: 0%	Gr 1: 18% Gr 2: 6% Gr 3: 2% Gr 4: 0%	Gr 1: 2% Gr 2: 4% Gr 3: 0% Gr 4: 0%	NR	60%	98%
Whole (32/38) partial (6/38)	Cyberknife timing NR	36.25 Gy/5 fx (24/38) [38.6 − 98.6 $Gy_{1.5}$]	Gr 1: 18.5% Gr 2: 7.4% Gr 3: 3.7% Gr 4: 0%	Gr 1: 4.5% Gr 2: 0% Gr 3: 0% Gr 4: 0%	Gr 1: 4.8% Gr 2: 9.4% Gr 3: 4.8% Gr 4: 0%	Gr 1: 9.5% Gr 2: 4.8% Gr 3: 0% Gr 4: 0%	86.8%	68.4%	NR

(continued on next page)

Table 1 (*continued*)

Partial versus whole prostate re-RT	Treatment delivery	Most common re-RT dose (EQD2 range, $\alpha/\beta = 1.5$)	Acute GU toxicity	Acute GI toxicity	Late GU toxicity	Late GI toxicity	LC	BRFS	OS
Whole (41/64) Partial (23/64)	VERO (54/64), other: RapidArc, Cyberknife treatment EOD	30 Gy/5 fx (31/64) 25 Gy/5 fx (27/64) [46.4 − 92.6 $Gy_{1.5}$]	Gr 1: 20% Gr 2: 5% Gr 3: 1.5% Gr 4: 0%	Gr 1: 8% Gr 2: 1.5% Gr 3: 1.5% Gr 3: 0%	Gr 1: 28% Gr 2: 9% Gr 3: 0% Gr 4: 0%	Gr 1: 6% Gr 2: 1.5% Gr 3: 1.5% Gr 4: 0%	71.9%	35.9%	92%
Whole	LINAC VMAT RapidArc Timing NR	25 Gy/5 fx (14/23) 0 Gy/5 fx (9/23) [46.4 − 64.3 $Gy_{1.5}$]	Gr 1: 43.5% Gr 2: 13% Gr 3: 4.4% Gr 4: 0%	Gr 1: 0% Gr 2: 0% Gr 3: 0% Gr 4: 0%	Gr 1: 17.4% Gr 2: 0% Gr 3: 4.4% Gr 4: 0%	Gr 1: 0% Gr 2: 0% Gr 3: 0% Gr 4: 0%	60.9%	34.8%	100%
Partial	Cyberknife treatment EOD	36 Gy/6 fx [77.1 $Gy_{1.5}$]	Gr 1: 25% Gr 2: 0% Gr 3: 0% Gr 4: 0%	Gr 1: 8.3% Gr 2: 0% Gr 3: 0% Gr 4: 0%	Gr 1: 8.3% Gr 2: 0% Gr 3: 0% Gr 4: 0%	Gr 1: 0% Gr 2: 0% Gr 3: 0% Gr 4: 0%	66.7%	50%	NR
Partial (51/100) Whole (49/100)	Cyberknife (81/100), other: VERO, RapidArc	36 Gy/6 fx (63/100) [46.4-90.6 $Gy_{1.5}$]	Gr 1: NR Gr 2: 8% Gr 3: 1% Gr 4: 0%	Gr 1: NR Gr 2: 0% Gr 3: 0% Gr 4: 0%	Gr 1: NR Gr 2: 16% Gr 3: 1% Gr 4: 0%	3-year ≥ grade 2 GI toxicity: 1%	90%	55%	96%
Partial	Cyberknife treatment 3 fractions/wk	36 Gy/6 fx [77.1 $Gy_{1.5}$]	Gr 1: 42.9% Gr 2: 21.4% Gr 3: 2.4% Gr 4: 0%	Gr 1: 4.8% Gr 2: 0% Gr 3: 0% Gr 4: 0%	Gr 1: NR Gr 2: 0% Gr 3: 0% Gr 4: 0%	Gr 1: NR Gr 2: 0% Gr 3: 0% Gr 4: 0%	100%	81%	NR

Abbreviations: 3D-CRT = 3D conformal radiation therapy; BRFS = biochemical relapse free survival; BT = brachytherapy; EBRT = external beam radiation therapy; EOD = every other day; EQD2 = equivalent dose in 2 Gy fractions; GI = gastrointestinal; Gr = grade; GU = genitourinary; IMRT = intensity modulated radiation therapy; IQR = interquartile range; LC = local control; LR = local recurrence; MRI = magnetic resonance imaging; NR = not reported; OS = overall survival; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; Pts = patients; re-RT = reirradiation radiation therapy; RP = radical prostatectomy; SBRT = stereotactic radiation therapy; VMAT = volumetric modulated arc therapy.

combination of imaging (typically positron emission tomography [PET] or magnetic resonance imaging [MRI]) with or without a biopsy. Of the 62.9% of patients who underwent biopsy before re-RT, 16 patients had a negative biopsy but a biochemical/radiographic local recurrence that was treated. One study included 9 patients with a limited number of oligometastatic sites treated with curative intent.[33] Ten studies used PET imaging before re-RT, and 6 studies had ≥95% of patients undergoing PET.[31,32,35-38]

The usage of ADT during initial RT, between initial RT and re-RT, and with re-RT is summarized in Appendix E2. ADT use was often not reported, particularly between initial RT and re-RT. Twelve of 13 studies reported ADT use with re-RT, with 30.1% (127 of 422) of patients receiving ADT with re-RT (with medians ranging from 6–17.8 months). No studies reported outcomes separately for those who received ADT and those who did not, nor did they publish their criteria for administering ADT. No studies mandated concurrent use of ADT with re-RT. No studies specified whether BRFS began after ADT was completed, and it was not possible to report outcomes separately for those who received ADT.

The median re-RT EQD2 was 77.1 Gy, using $\alpha/\beta = 1.5$, corresponding to 36 Gy in 6 fractions. Most patients (92%) were treated with SBRT, with doses typically ranging between 25 to 36.25 Gy in 5 to 6 fractions. Cyberknife was the most commonly used re-RT platform in 68.7% of patients. Partial prostate re-RT or hemi-prostate re-RT was used in 52.1% of patients, with the remainder receiving whole prostate re-RT (with or without a boost).

Some, but not all studies used a CTV expansion on the gross target volume in partial prostate radiation up to 5 mm. Planning target volume (PTV) expansions ranged from 0 mm to 5 mm (3 mm posterior). Scher et al[38] used a rectal spacer in 23 patients, and although significantly lower rectal doses were achieved, no differences in acute and late toxicities were found. Pasquier et al[37] used a rectal spacer in 9 patients without reporting separate outcomes.

Oncologic outcomes

The random effects LC was 83.2% (95% confidence interval [CI], 75.5%-90.9%; Fig 2a) with significant heterogeneity ($I^2 = 85\%$, Q test $P < .001$). Meta-regression found that increasing EQD2 (regression coefficient 0.006, $P = .05$) and decreasing length of follow-up (regression coefficient −0.006, $P = .002$) were associated with improved LC, but whole versus partial prostate re-RT was not associated with LC ($P = .567$). As highlighted previously, it was not possible to analyze oncologic outcomes by ADT utilization due to incomplete reporting of ADT in the included literature.

The random effects BRFS was 59.3% (95% CI, 47.9%-70.7%; Fig 2b) with significant heterogeneity ($I^2 = 83\%$, Q test $P < .001$). Meta-regression found that increasing EQD2 (regression coefficient 0.011, $P = .001$) and decreasing length of follow-up (regression coefficient −0.006, $P = .001$) were associated with improved BRFS, but not whole versus partial prostate re-RT ($P = .484$).

Meta-regression of studies using SBRT found increasing EQD2 was associated with LC (regression coefficient 0.009, $P = .015$) and BRFS (regression coefficient 0.012, $P = .02$), with no effect of length of follow-up (LC: $P = .929$; BRFS: $P = .576$) or whole versus partial prostate re-RT (LC: $P = .866$; BRFS: $P = .498$).

Distant metastasis free survival was infrequently reported and ranged from 70.6% to 100%. Overall survival ranged from 76% at 8 years follow-up to 100% with shorter follow-up.

Reported toxicities

Reported severe acute toxicity was rare, with only 6 episodes of acute grade 3 GU toxicity and no instances of acute grade 3 GI toxicity. Rates of acute ≥grade 2 toxicity were 10.5% (95% CI, 5.5%-15.4%) for GU and 1.1% (95% CI, 0.1%-2.0%) for GI.

Reported late toxicity (greater than 3 months after completion of re-RT) was rarely observed in most studies, noting that the majority of included studies had insufficient length of follow-up, which precludes definitive statements on rates of late toxicities. Reported late GU toxicity ≥grade 3 occurred in 3.4% of patients (95% CI, 1.0%-5.8%; Fig 3a), with moderate heterogeneity ($I^2 = 49\%$, Q test $P = .024$). Meta-regression found increasing EQD2 (regression coefficient 0.004, $P = .001$), increasing length of follow-up in months (regression coefficient 0.003, $P = .006$), and whole prostate re-RT (regression coefficient −0.088, $P < .001$) were predictive of late GU toxicity ≥grade 3.

Late GI toxicity ≥grade 3 occurred in 2.0% of patients (95% CI, 0.1%-4.0%; Fig 3b), with significant heterogeneity ($I^2 = 57\%$, Q test $P = .006$). Meta-regression found increasing EQD2 (regression coefficient 0.002, $P = .014$), increasing length of follow-up in months (regression coefficient 0.003, $P = .002$), and whole prostate re-RT (regression coefficient −0.033, $P = .04$) were predictive of late GI toxicity ≥grade 3.

Meta-regression of studies using SBRT found no effect of EQD2 (GU: $P = .343$; GI: $P = .857$), length of follow-up (GU: $P = .995$; GI: $P = .932$), or whole versus partial prostate re-RT (GU: $P = .243$; GI: $P = .952$) on late ≥grade 3 toxicity.

Detailed information on ≥grade 3 GU/GI events is available in Appendix E3. No grade 5 toxicities occurred. Severe toxicity tended to be observed with EBRT rather than SBRT, with 50% (10 of 20) of late GU toxicities and 100% (10 of 10) of ≥grade 3 late GI toxicities observed with EBRT, despite only comprising 8% of patients. However, studies with EBRT had longer-term follow-up.

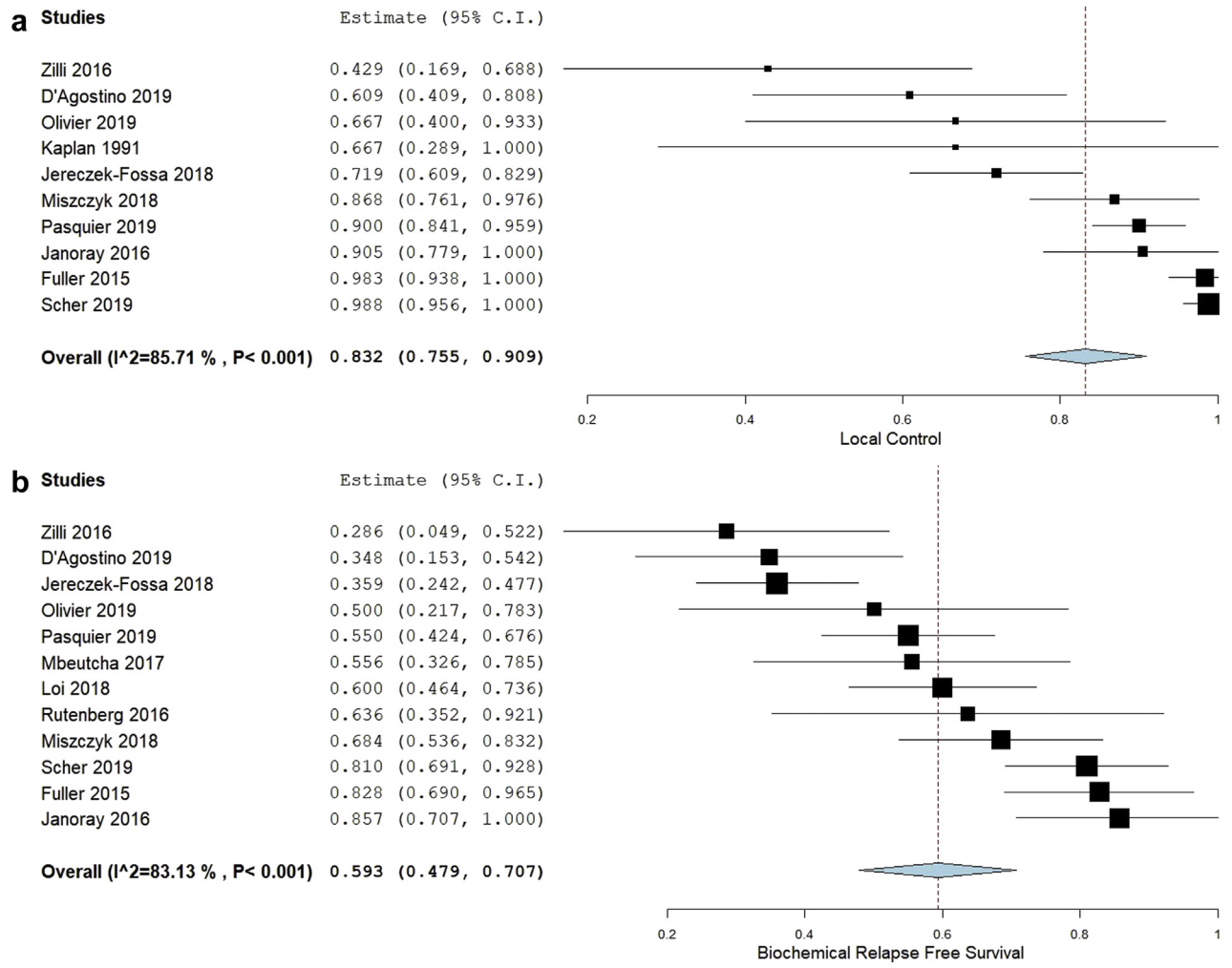

Figure 2 (a) Forest plot of local control in included studies. (b) Forest plot of biochemical failure-free survival in included studies.

Intact prostate Re-RT

Twelve studies included a total of 344 patients who had an intact prostate (ie, had not received an RP) and had received salvage re-RT. Nine studies with 267 patients provided separate oncologic and toxicity outcomes. Among these patients, oncologic and toxicity profiles were similar to the entire cohort. LC was 88.0% (95% CI, 80.2%-95.8%) and BRFS was 61.6% (95% CI, 47.3%-76.0%). Acute grade 2 toxicity was observed in 30 patients (GU) and 6 patients (GI). Acute grade 3 GU toxicity was observed in 3 patients. Late GU toxicity ≥grade 3 occurred in 4.5% of patients (95% CI, 0.6%-8.5%) and late GI toxicity ≥grade 3 occurred in 3.8% of patients (95% CI, 0.0%-7.5%).

Prostate bed re-RT

Seven studies included a total of 84 patients who underwent RP, whole prostate bed RT, and subsequent partial prostate bed SBRT re-RT. Four studies with 50 patients provided separate oncologic and toxicity outcomes and found 24 episodes of biochemical failure (52% BRFS), of which 13 were within the prostate bed (74% LC). Treatment was well tolerated with no new acute or late grade ≥3 toxicity due to re-RT. Acute grade 2 toxicity was observed in 4 patients (GU) and 1 patient (GI). Late grade 2 toxicity was observed in 6 patients (GU) and 1 patient (GI).

Organs at risk

A summary of organs at risk (OAR) constraints used for bladder and rectum is presented in Appendix E4. Dose-volume histogram information in the cohort published by Zilli was analyzed by Dipasquale et al[44] to predict GI toxicity. This identified increasing cumulative D1cc (minimum dose to 1 cm^3 of the most irradiated volume) to the rectum was associated with grade 3/4 GI toxicity, and staying below a combined threshold of 130 Gy ($\alpha/\beta = 3$) may be a reasonable target.

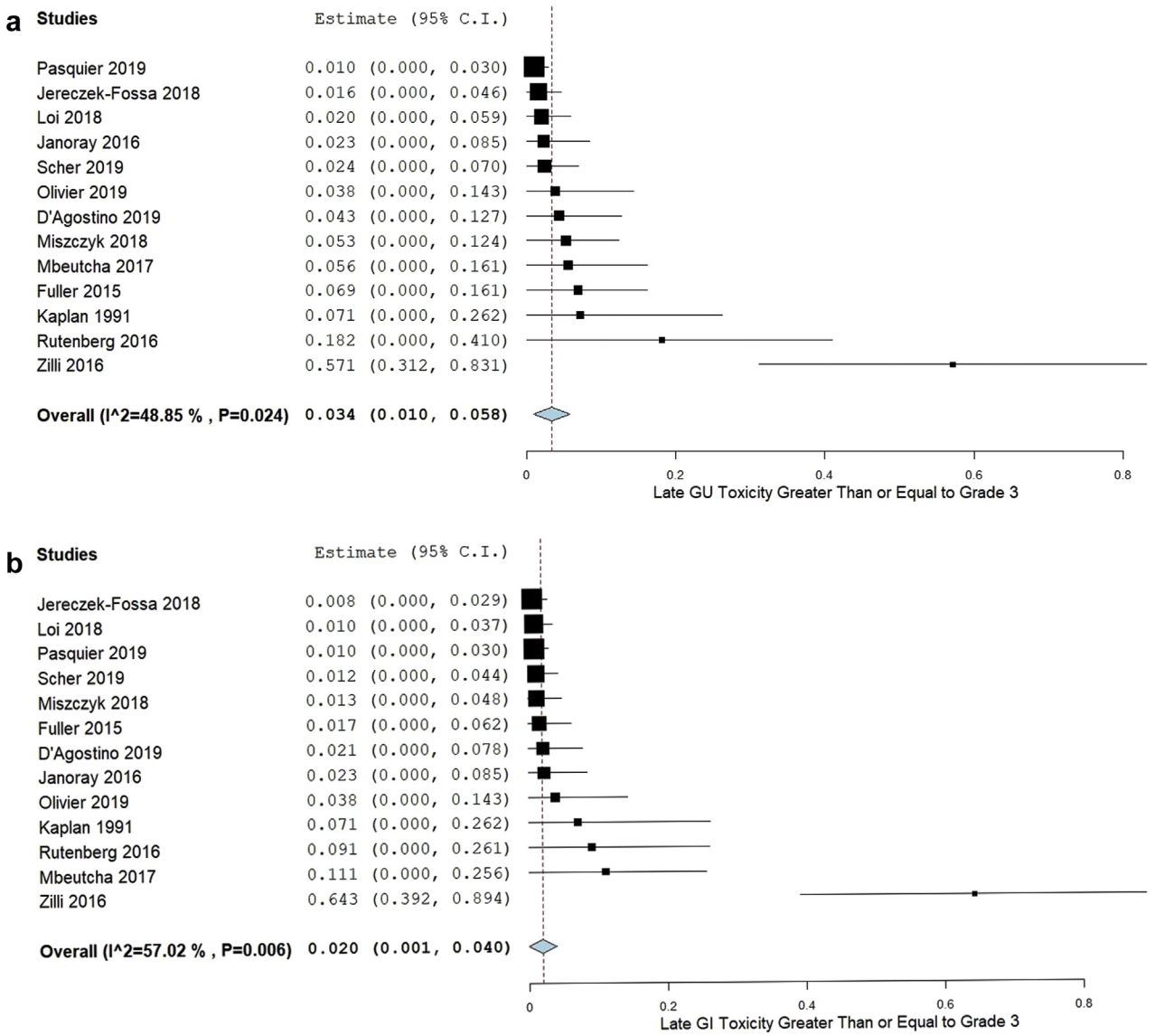

Figure 3 (a) Forest plot of late genitourinary (GU) toxicity greater than or equal to grade 3 toxicity. (b) Forest plot of late gastrointestinal (GI) toxicity greater than or equal to grade 3 toxicity.

Discussion

Our review shows the emerging role of using EBRT and SBRT re-RT as local salvage in prostate cancer. With short-term follow-up, local and biochemical control appear reasonable, with the majority of studies achieving this through manageable acute and early reports of late toxicity. SBRT was the most common re-RT treatment strategy in the literature, and based on relatively low late GU and GI side effects in our review, appears to be the optimal EBRT re-RT strategy. However, considerable variation among the available series precludes a single preferred delivery and dose/fractionation scheme. Our study results are limited by the short-term outcomes reported in the included literature and incomplete reporting of ADT use, precluding definitive statements on long-term oncologic outcome and long-term toxicity.

As with any salvage treatment for prostate cancer, patient selection remains of the utmost importance. Patient characteristics can predict localized recurrence post-RT, such as low-risk disease at diagnosis, pretreatment PSA velocity <2.0 ng/mL per year, disease-free interval >3 years, and PSA doubling time >12 months.[9] PSA doubling times of less than 3 or 6 months is a poor prognostic factor for distant metastatic disease and prostate cancer mortality.[45,46] Improvements in prostate cancer imaging with multiparametric MRI (mpMRI) and PET may help identify isolated local recurrence and exclude metastatic disease, particularly with PSA levels ≥ 2 ng/mL.[47-50] Previously proposed selection criteria for local salvage include (1) biopsy proven recurrence, (2) no metastatic disease, (3) reasonable urinary function (International Prostate Symptom score of less than 20), (4) greater than 5-year life expectancy, (5) disease-free

interval >2 years, (6) PSA doubling time greater than 6 months, (7) Gleason score ≤6, and (8) PSA of less than 10 at recurrence.[51] We propose modification to these criteria by carefully considering re-RT in those with Gleason scores greater than 6 (though caution should be used in those with initial high-risk disease). The emergence of metastasis-directed therapy for men with oligometastatic prostate cancer raises the possibility of SBRT +/- ADT as an investigational salvage strategy for both local and limited distant metastases.[52,53]

Our review included several studies that did not mandate confirmatory biopsies, and none specified whether mapping biopsies were performed. Transperineal prostate biopsies would be the ideal technique to confirm isolated local recurrence, allowing for both sampling of the suspicious local recurrence as well as mapping biopsies including the anterior zone. In de novo prostate cancer, the anterior zone contains disease and isolated disease 52.7% and 10% of the time, respectively.[54] Although most recurrences occur at the dominant intraprostatic lesion, some men have radiorecurrent prostate cancer in areas previously biopsied as negative at their primary radiation.[55] PET and mpMRI may be useful as guidance for targeted biopsies, but we are unaware of data to support omitting biopsies.

We found increasing EQD2 was associated with improvements in LC and BRFS in our meta-regression, mirroring results of dose escalation in primary prostate cancer.[56] Two studies in our review also found improved BRFS when a BED of ≥130 Gy ($\alpha/\beta = 1.5$, ≥30 Gy in 5 fractions, 85% vs 60%, $P = .0006$)[34] and >120 Gy ($\alpha/\beta = 2$, >30 Gy in 5 fractions, hazard ratio 0.41, 95% CI, 0.20–0.86, $P = .018$) was used.[37] This supports the notion that a therapeutic dose of RT should be considered in re-RT. Decreasing length of follow-up was associated with improvements in LC and BRFS, in addition to decreased late toxicity rates, suggesting that outcomes reported in our review are not mature and longer follow-up is necessary before definitive statements can be made.

We found no improvement in LC or BRFS with whole prostate re-RT, and severe late toxicity was less frequent with partial prostate re-RT on meta-regression. Caution must be used in patient selection for partial prostate re-RT to confirm that all sites of disease in the prostate are appropriately identified and treated. Only 1 study has evaluated radiorecurrent prostate cancer with whole mount salvage RP and mpMRI,[57] which found tumor extent was underestimated with mpMRI, and multifocal recurrence occurred in almost all patients. This supports adding a CTV margin to the mpMRI delineated gross target volume and using mapping biopsies before re-RT. Given that recurrences after brachytherapy were often smaller and involved the seminal vesicles, different primary RT techniques (EBRT, SBRT, or brachytherapy) may require different target delineation and salvage strategies.

In comparison to other salvage treatments for local failure of prostate cancer, re-RT appears to have infrequent short-term toxicity. Assessment of late severe GU/GI toxicity is limited by short-term follow-up, with increasing length of follow-up associated with an increased likelihood of late GU/GI toxicity (noting that older studies also used less sophisticated re-RT techniques). The rates of reported late GU and GI toxicity appear to be lower than reported in prospective randomized studies of initial definitive therapy,[58,59] which may be due to misattribution of toxicity in retrospective studies as well as the limited follow-up. None of the included studies reported patient-reported outcomes. Although other salvage therapies for radiorecurrent prostate such as radical prostatectomy, cryotherapy, HIFU, and brachytherapy are better established with long-term follow-up, similar oncologic outcomes have been reported between surgical and nonsurgical approaches.[60]

One study stands out for having severe longer-term ≥grade 3 toxicity combined with poor local and biochemical control.[28] These patients were often first treated with 2-dimensional RT, followed by re-RT with 3D-conformal RT, with many receiving a brachytherapy boost. Despite extremely high doses of reirradiation, the poor oncologic outcomes may ultimately be partly due to patient selection (median PSA at re-RT of 7.4 ng/mL), reflective of a high probability of subclinical metastatic disease despite 78.6% of patients undergoing PET before salvage. The toxicity may also reflect an interaction between high volumes of normal tissue undergoing re-RT with EBRT followed by a focal injury with brachytherapy in a majority of cases. These findings should be carefully considered before embarking on salvage re-RT, as this represents the only cohort with mature long-term follow-up, and late GU/GI toxicity was observed many years after treatment. By incorporating image guidance, fiducials, smaller PTV margins, and inverse planning with SBRT, the expectation is that longer term follow-up will confirm the encouraging early toxicity results with SBRT; however, this remains to be demonstrated.

Our review is limited by heterogeneous methodologies of the included studies. As the majority of studies were retrospective, toxicity may be underreported or misattributed. Of the 13 included studies, 6 had a median follow-up of fewer than 24 months, which is likely not sufficiently long to evaluate the full effect of late GU/GI toxicity. The usage of ADT during re-RT likely resulted in overestimation of oncologic outcomes in our review, as 30.1% of patients received ADT with re-RT. This limitation could not be accounted for statistically due to limitations of the primary literature, and we encourage future authors in this area to report outcomes separately by ADT utilization and duration. Our review was not able to assess re-RT plan quality and whether it is

necessary to compromise target volume coverage for OAR.

To establish re-RT using SBRT as a standard salvage treatment for local failure in prostate cancer, prospective studies evaluating short- and long-term toxicity along with oncologic outcomes are needed. PET, mpMRI, and mapping biopsies to accurately define the extent of local recurrence should be incorporated. SBRT should be planned and delivered using a standardized approach incorporating fiducials for management of intra- and inter-fraction error and enabling small PTV margins, consistent dose-fractionation prescriptions, and strict adherence to OAR constraints. Although no definitive conclusions can be drawn, partial prostate reirradiation is increasingly being explored as a technique to minimize normal tissue reirradiation. Rectal sparing strategies such as endorectal balloons or gel tissue spacers could also be incorporated with either whole gland or focal re-RT as another toxicity reduction strategy. The recently published phase I/II Genitourinary Group, French Association of Urology 31 protocol appears to be incorporating many of these principles and is prospectively accruing patients for partial prostate re-RT using SBRT without ADT in appropriately selected patients.[61] This study protocol mandates use of confirmatory biopsy, fiducials, MRI, PET, and a 2 mm PTV margin. These are similar principles to contemporary studies reporting favorable salvage outcomes with partial prostate high dose rate brachytherapy.[62] It remains to be seen whether ADT should be incorporated in the locally radiorecurrent or oligometastatic setting. Finally, optimal patient selection for those men with isolated local recurrence using next generation imaging is recommended.[63] In the interim, although salvage re-RT using EBRT, particularly using SBRT, appears to be a promising technique, we believe that this technique should be limited to clinical trials until long-term toxicity data are established, ideally through prospective trials comparing this approach against other salvage strategies.

Supplementary data

Supplementary material for this article can be found at https://doi.org/10.1016/j.adro.2020.04.022.

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