Salvage stereotactic body radiation therapy for locally recurrent prostate cancer following primary radiation therapy, are benefits worth toxicity risk?: A systematic review

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Abstract

Salvage stereotactic body radiation therapy (SBRT) for local prostate cancer recurrence following radiation therapy remains controversial. Salvage SBRT may cure disease recurrence however receives criticism as it carries with it risks of severe genitourinary and gastrointestinal toxicity. We performed a systematic review to assess the efficacy and side effects profile of salvage SBRT for locally recurrent prostate cancer to assess the role of salvage SBRT in clinical practice. A systematic review was carried out using Pubmed (MEDLINE) and Scopus databases. Inclusion and exclusion criteria were satisfied, and those studies included were quality assessed using the ROBINS-I checklist. Five studies in total met criteria for inclusion. Median doses for SBRT ranged from 30Gy to 36Gy delivered over 5 to 6 fractions. Recurrence free survival ranged from 40% to 76% at 2 years. Genitourinary toxicity was more prevalent than gastrointestinal toxicities. Grade 2 and 3 genitourinary complication rates ranged from 5 – 22% and 0 to 9% respectively. Gastrointestinal grade 2 complication rates ranged from 0 to 11% and no grade 3 complications were recorded. Lower dose SBRT generally was associated with less gastrointestinal and genitourinary side effects however had inferior recurrence free survival rates. This systematic review serves as one of the first to characterise SBRT as a salvage option for locally recurrent prostate cancer. Further large-scale prospective studies are required to guide whether the benefits outweigh the risk profile.

Background

Prostate cancer recurrence following definitive radiation therapy remains a significant health concern. Despite the advances in the array of radiation modalities, local control continues to remain elusive with biochemical failures occurring in up to 40-60% of patients following external beam radiation therapy (EBRT)[1]. Biochemical failure following EBRT is defined as a value exceeding the post treatment nadir by >2 ng/mL or three consecutive rising prostate specific antigen (PSA) tests. Patients who fail EBRT, will go on to require some form of salvage therapy; this can be local or systemic. Systemic salvage treatment is used in the vast majority of cases and consists of androgen deprivation therapy (ADT). While often having good initial biochemical response, prostate cancer will ultimately develop castrate resistance in most instances from 2-3 years[2]. ADT is also responsible for side effects including loss of libido, hot flushes, muscle loss, osteopenia, insulin resistance, obesity and cardiovascular disease which can result in severe cardiac events and death[3]. Seeking a safe and effective local salvage therapy would substantially change and improve the management of biochemical recurrent prostate cancer post EBRT in select patients.

The current local salvage therapy options include radical prostatectomy (RP), brachytherapy, high intensity focussed ultrasound (HIFU), cryotherapy and stereotactic body radiotherapy (SBRT). While these wide assortment of local salvage options are available, they remain infrequently used in only 2% of cases given their increased perceived toxicity and local side effects to tissues brought about by the preceding radical dose of radiation[4]. Stereotactic body radiation therapy is one such technique becoming used as a salvage technique however its efficacy and safety profile remains a contentious issue.

There has recently been a number of systematic review articles in the literature assessing salvage options for locally recurrent prostate cancer[5-7]. These articles have included a wide array of slavage techniques ranging from radical prostatectomy, high intensity frequency ultrasound (HIFU), cryotherapy, brachytherapy and to an extent SBRT. Overall, these reviews tended to report improve toxicities from salvage non-surgical options compared to RP. Biochemical control rates seemed to be more favourable in salvage brachytherapy and EBRT cases but ultimately more long-term prospective trials were needed to improve the quality of these articles. While SBRT is touched on in a small number of these systematic review articles there remains no systematic review in the literature which focusses on a further in-depth analysis of salvage SBRT following radiation therapy for locally recurrent prostate cancer. To the best of our knowledge, we contribute the first systematic review to focus on salvage SBRT in locally recurrent prostate cancer post definitive radiation therapy.

Methods

Evidence acquisition

We carried out a systematic review of the literature in the databases Pubmed (MEDLINE) and Scopus. The search date included studies from conception to October 2021. This systematic review was conducted according to the published Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. The review was registered in the PROSPERO database.

Search strategy

The systematic search process was undertaken by two authors (G.B and A.B). Search results were restricted to English language. Search strategy for both Pubmed and Scopus included the following key words arranged in variable combinations; “Prostate” OR “prostate cancer” OR “prostatic adenocarcinoma” AND “salvage” OR “recurrent” OR “biochemical recurrence” OR “local failure” AND “SBRT” OR “stereotactic body radiation therapy” OR “SABR” OR “cyberknife” OR “re-irradiation” AND “EBRT” OR “external beam radiation therapy” OR “radiation”.

Quality assessment

This systematic review utilised the ROBINS-I checklist quality assessment tool for non-randomized studies. The details of this checklist are shown in table 1.

Inclusion criteria

Studies were eligible if they met the following inclusion criteria. Population consisted of patients with local recurrence in prostate cancer. Studies that assessed patients who underwent external beam radiotherapy as their primary definitive modality of prostate cancer treatment. Patients who subsequently underwent stereotactic body radiotherapy (SBRT) as their salvage therapy. Exclusion criteria included metastatic prostate cancer, prostate cancer initially treated with modalities other than EBRT such as

radical prostatectomy, brachytherapy etc. Review studies, studies not in English and studies where the full original article was not accessible were also excluded. Any discrepancy between the two authors was resolved via consensus.

Outcomes

Primary endpoints were the recurrence free survival rates. Secondary endpoints were side effect profiles, toxicity and complication rates following salvage SBRT.

Results

Study characteristics

A total of 598 articles were found through Pubmed (MEDLINE) and scopus. Five studies were included in our systematic review after a screening process of the inclusion and exclusion criteria (*Figure 1*). All the studies included were deemed to have acceptable quality control based on the ROBINS-I tool (*Table 1*).

Patient characteristics prior to salvage SBRT

Patient characteristics can be seen in *Table 2*. Pasquier et al 2019[8] performed a relatively large multi-centre retrospective study assessing salvage SBRT on patient primarily treated with EBRT. The study consisted of 100 patients which at this time was the largest retrospective study carried out. The median age from this cohort of their initial prostate cancer diagnosis was 62 years of age. The median PSA at this time was 10.2 and in this study 80% of the cohort underwent EBRT only with a modest proportion having brachytherapy (17%) and EBRT in addition to brachytherapy (3%). Of those treated with definitive EBRT, a median dose of 74 Gy was used with a median fraction of 37. The median age of recurrence was 71.2 years of age. Median PSA at recurrence was 4.3 and this was associated with a median PSA doubling time of 12 months. Confirmation of localised recurrence was confirmed with biopsy in 75% of cases which are displayed in table 2. Where biopsy was not carried out, MRI and PET imaging was used to confirm recurrence of disease.

Leroy et al 2017[9] performed a retrospective single centre study with a sample size of 23 patients. Of these patients, 83% underwent EBRT as their primary definitive cancer treatment. The study also included other radiation therapy (RT) modalities including brachytherapy and also included patients undergoing ADT (61%).

Mbeutcha et al 2017[10] retrospectively reviewed records of a total of 28 patients who previously underwent EBRT or LDR brachytherapy for primary prostate cancer definitive intervention. This study assessed both SBRT and HDBT comparatively however for our analysis, we only reviewed those patients in the salvage SBRT arm which totalled a sample size of 18 patients. This was ultimately the smallest of the studies reviewed. Of our patients of interest it is important to note that only 17% of them had EBRT as

their primary definitive radiation therapy. Median age for patients at biochemical recurrence was 69. These patients had a median PSA of 4.5.

The retrospective study carried out by Jereczek-Fossa[11] in 2018 was at the time of publication was the largest study which compared salvage SBRT for locally recurrent prostate cancer following primary EBRT, BRT or salvage post-prostatectomy RT. Median age at recurrence (73.2) was marginally higher in this cohort in comparison with the literature. At this diagnosis a median PSA was reported at 3.89 and only 44% went on to have biopsy proven recurrence. In these non-biopsy patients, local recurrence was diagnosed with PSA levels with imaging assistance by PET and CT and/or MRI.

Fuller 2020 performed a prospective non-controlled clinical study of 50 patients. This study was the only prospective study meeting criteria for this systematic review. The study was carried out over a 9-year period in patients with biopsy proven locally recurrent prostate cancer post radiation therapy. To allow for more accurate complication assessment, patients were excluded from the study if they reported greater than grade 1 toxicity from the original radiation therapy course. Patients with recurrent disease spread beyond the peri-prostatic region was also excluded. Patients included in this study had a median prior radiation dosage of 75.6 Gy and the median interval to salvage treatment was 98 months. 92% of the population of the study had undergone conventional radiation therapy while the remaining had undergone other methods including brachytherapy, SBRT and prostatectomy with adjunct EBRT. Median PSA at recurrence was reported at 3.97 and 14% of these cases were on concurrent ADT.

Details of stereotactic body radiation therapy utilised

The characteristics of SBRT used by each study are summarised in *Table 3.* Pasquier et al 2019[8] had a median follow-up of 29.3 months which was one of the shortest follow up intervals recorded. The dosage of SBRT utilised for this study comprised of 35-36.25 Gy in 5 and 6 fractions resulting in a biological effective dosage (BED) of >120 Gy in 77% and a BED of ≤120 Gy in the remaining 23 patients. With this regime, median nadir PSA was 0.5 in this population which was obtained over a median period of 10.3 months (1.5-40.8) from salvage SBRT. For patients without adjunctive ADT, this nadir PSA was 0.71 after a median period of 11 months.

Leroy et al 2017 utilised Cyber-Knife SBRT in which a total dose of 36Gy delivered over 6 fractions was utilised. Fiducials were implanted prior to all cases. The majority of these cases having irradiation of the whole prostate gland (83%). Treatment was delivered every other day during 12-14 days where real-time tracking of the intra-fraction was used.

Mbeutcha et al 2017 delivered salvage SBRT with a Cyberknife® accelerator. Fiducials were used as well as pre-treatment computerised tomography (CT), Magnetic resonance imaging (MRI) and/or choline positron emission tomography (PET) to define prostate index tumour. A dose of 35Gr over 5 fractions delivered radiation to focal targets of prostate. Unlike many of our reviewed articles, this study only utilised focal radiation therapy, there was no whole gland irradiation.

Jereczek-Fossa et al 2018 utilised a extreme hypofractionation in majority of patients with a median dose of 30Gy given in five fractions. SBRT involved Cyberknife® (5%), VERO® (84%) and Trilogy® (11%). Salvage SBRT was performed for intraprostatic recurrence and for post-prostatectomy bed recurrence in 70% and 30% of cases respectively. Included in this cohort undergoing salvage SBRT, 25% were on concurrent ADT therapy.

The prospective study by Fuller et al 2020 employed MRI to define prostate margins and extra prostatic extension utilising a protocol dose of 34 Gy given in 5 daily fractions of 6.8 Gy. Dosing covered >95% of the PTV prescribed dose to deliver “HDR-like” peripheral zone dose escalation. This was carried out with fiducial based CyberKnife SBRT technique. Toxicities were assessed with the CTCAE v3.0 criteria.

Recurrence free survival and efficacy of salvage therapy

The survival rates and efficacy of salvage SBRT are summarized in table 4. Pasquier et al reported median bounce value of 1.8 was obtained after a median period of 20.2 months after re-irradiation. True recurrence free survival rates at 2 years were 73% (95% confidence interval [CI] 62%-81%) and at 3 years were 55% (95% CI, 42%-66%). The overall survival rates at 2 and 4 years were 96% and 94% respectively. Of these patients with recurrences 10 had intra-prostatic recurrences and 7 were found to have extra pelvic metastatic disease, there was one death from prostate cancer.

Leroy et al 2017 found in patients with recurrent prostate cancer following EBRT, salvage SBRT was able to limit disease progression in 61% of cases and recorded a 2 year disease-free survival of 54%. Median disease free survival was 27 months (CI 95%).

Within a median follow up of 14.5 months, Mbeutcha et al 2017 found 55.6% of those following salvage SBRT remained bNED. 72.2% experiences regression of PSA, 11% experienced stabilisation of PSA and 16.7% experienced post-SBRT biochemical failure. Of these patients who experienced this biochemical failure post-SBRT, they were found to have developed subsequent extra-prostatic evolution despite even ADT therefore indicating an advanced and refractory disease.

Jereczek-Fossa et al 2018 observed 64% of patients following salvage SBRT had progressive disease by a median time of 26.1 months. The median time to progression of disease was 14 months (range: 3.1-65.9). This appeared to be unrelated to whether a patient had SBRT to the prostate bed or prostate gland itself. Relapse rates however were slightly higher (non-significant) in patients with a prior prostatectomy who had SBRT to their prostate bed compared to those with gland irradiation. The 2-year biochemical progression free survival was the lowest of all studies included at 40%. Overall cancer specific survival at 2 years 95%. The adjunct of ADT interestingly was associated with higher biochemical progression compared to those without ADT (75% vs 52%).

The study by Fuller et al 2020 employed a median 44 month follow up protocol which found the median PSA level at 1 and 5 years to be 0.6 ng/mL and 0.16 ng/mL respectively. Two and five year biochemical recurrence free survival rates measured 76% and 60% respectively. The five year local and distant relapse-

free rates measured 94% and 89%, respectively. The study found risk factors for relapse included higher pre-salvage PSA levl was associated with greater risk of relapse. The median pre-SBRT PSA of relapse vs relapse free groups was found to be 7.11 ng/mL vs 2.99 ng/mL (p=0.0006). Specifically, a PSA level of 6.92 ng/mL was calculated to be the sharpest cut-off value, with actuarial 5-year relapse-free rates of 78% vs 12% for those patients in the study who had pre-salvage SBRT PSA levels of above or below this respectively.

Genitourinary complications and adverse events

GU toxicity rates are summarized in table 4. Pasquier et al recorded rates grade 2 and 3 acute genitourinary (GU) adverse events of 8% and 1% respectively. At 3 years, chronic GU toxicity of grade ≥ 2 was 20.8% (95% CI, 3.1%-29.7%). These included cystitis and pain on micturition (10%), urinary retention (1%), haematuria (2%), and incontinence (3%). A BED of greater than 120Gy was positively associated with late grade ≥2 adverse events on univariate analysis (P=.007). There did not appear to be association with volume of prostate treated and toxicity rates. Moreover, no differences in toxicity rates were seen comparing prior EBRT vs brachytherapy.

Leroy et al 2017 found that overall treatments were well tolerated. Grade 1, 2 and 3 GU complications were found in 48%, 22% and 9% respectively. These included cystitis (65%), urethral stenosis (8.7%), dysuria (9%) and urethritis (4.3%). The study found no correlation between the dosimetric factors, previous treatment toxicities or post-SBRT treatment. In contrast with Pasquier et al, this study found whole gland irradiation was associated with more grade ≥ 2 toxicities (58% vs 0%) compared to less than whole gland SBRT.

In Mbeutcha et al study, they found the rates of acute GU toxicities following SBRT were 28% and 11% for grade 1 and 2 CTCAE. No grade 3 or 4 acute toxicities were recorded. Grade 1 late toxicities were found in 22% of cohort, grade 2 in 6%, no grade 3 and 6% with grade 4.

Jereczek-Fossa et al 2018 reported 72% of patients reported no acute GU complications. Grade 1, 2 and 3 complications were reported in 20%, 5% and 1.5% respectively. 1.5% were not evaluated. 57% of patients were without chronic GU complications (6 - 36 months). Grade 1, 2 and 3 GU chronic complications were present in 28%, 9% and 1.5% respectively. 3% were not evaluated. Overall, irradiation to the prostate bed as opposed to prostate gland was associated with more grade 2 complications (p=0.002).

The prospective study by Fuller et al excluded those patients who experienced > grade 1 GU complications and so compared to other studies reviewed had relatively low rates of GU complications. Acute toxicity was overall very mild where only 2% experienced urinary retention. They found no grade 3 or higher complications. There was some reported increased I-PSS scoring following salvage SBRT from 6 (presalvage) to 11/35, however this generally returned to pre-salvage baseline by 3 years. Late toxicities were recorded to be 17% and 8% for grade 2+ and 3+ complications respectively.

Gastrointestinal complications and adverse events

GI toxicity rates are summarized in table 4. Pasquier et al reported that no patients of their study presented acute GI adverse events of grade >1. At 3 year follow up, 1% of patients developed grade ≥ 2.

Leroy et al 2017 recorded grade 1, 2 and 3 GI complications in 8.7%, 8.7% and 0% respectively. Consistent with other studies reviewed that with SBRT, GI toxicities appear to generally be much lower compared to the GU toxicities seen.

Regarding GI complications, Mbeutcha et al 2017 recorded rates of acute toxicities to be 6% and 11% for grade 1 and 2 adverse events respectively. The only late GI toxicities were grade 2 found in 6%. No Grade 3 or 4 complications were recorded.

Similar to other studies evaluated, Jereczek-Fossa et al 2018 reported less frequent GI complications from SBRT compared with GU complications. 90% of patients had no acute GI complications. 8% and 2% of patients developed grade 1 and 2 GI complications respectively.

Fuller et al 2020 did not find any acute or chronic salvage SBRT toxicities above grade 1.

Discussion

We report herein the first systematic review to perform a focussed, up to date and in-depth analysis of SBRT as a salvage therapy for locally recurrent prostate cancer following radiation therapy. In this review we highlight the promising role of SBRT used as a salvage therapy for locally recurrent prostate cancer with acceptable genitourinary and gastrointestinal side effects. Conclusions from this systematic review should be interpreted with caution for several reasons. Firstly, salvage SBRT in many centres world-wide is not even considered as a salvage option in patients who have previously undergone EBRT. This results in a small number of acceptable quality papers that can be included in the systematic review. Secondly, the studies included were often heterogenous and therefore made meta-analysis not possible. However, despite these limitations, we successfully highlight the efficacy and safety profile of this modality as a viable option for locally recurrent prostate cancer.

International recommendations regarding re-irradiation therapy remain controversial. The clinical practice guidelines for both the National Comprehensive Cancer Network (NCCN) and the American Society for Radiation Oncology (ASTRO) do not currently recommend the use of salvage re-irradiation with SBRT for locally recurrent prostate cancer. From a urological perspective, the European association of urology (EAU) guidelines only recommend the use of salvage SBRT following previous radiation therapy only be undertaken in a clinical-trials setting[12]. The hesitancy in adoption of salvage re-irradiation SBRT by these governing bodies appear to largely be from the concerns raised regarding the potential for severe toxicities.

SBRT was seen to cause more genitourinary toxicity compared to gastro-intestinal toxic effects. Genito-urinary grades two and above are considered significant where intervention is required. This includes obstruction/stricture, fistula, cystitis or incontinence. Among the included studies, grade two GU toxicities

ranged from 2–22%. Grade three toxicities were observed in 0–9%. It is therefore evident that re-irradiation is likely associated with an increased rate of GU and GI complications to primary radiation therapy. Whether these risks outweigh the benefits however remain to be elucidated. Our data indicates that salvage SBRT is effective as a salvage therapy with five-year recurrence free survival rates at two and five years are up to 76% and 60% respectively for locally recurrent prostate cancer.

Conclusion

Salvage SBRT remains a controversial topic, largely due to the perceived increased toxicity to the local tissues from the re-irradiation therapy. Our systematic review highlights the actual rates of GU and GI toxicity and highlights an improved recurrence free survival. Further prospective trials in this domain are needed before salvage SBRT is adopted into current clinical practice.

Abbreviations

SBRT: Stereotactic radiation therapy
PSA: Prostate specific antigen

GI: Gastrointestinal

GU: Genitourinary

Gy: Gray

EBRT: External beam radiation therapy

ADT: Androgen deprivation therapy

HIFU: high intensity frequency ultrasound

PRIMSA: Preferred reporting items for Systematic reviews and meta-analyses

MRI: Magnetic resonance imaging

CT: Computerised tomography

PET: Positron emission tomography

Declarations

Ethics approval and consent to participate:

Not applicable

Consent for publication:

Not applicable

Availability of data and materials:

All datasets generated during the current study are included in the published article.

Competing interests:

The authors declare that they have no competing interests.

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Authors' constributions:

GB was involved with topic selection, data collection and writing of this systematic review. AB was involved with screening and data collection of articles. Both authors read and approved the final manuscript.

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Tables

Tables 1 to 4 are available in the Supplementary Files section

Figures

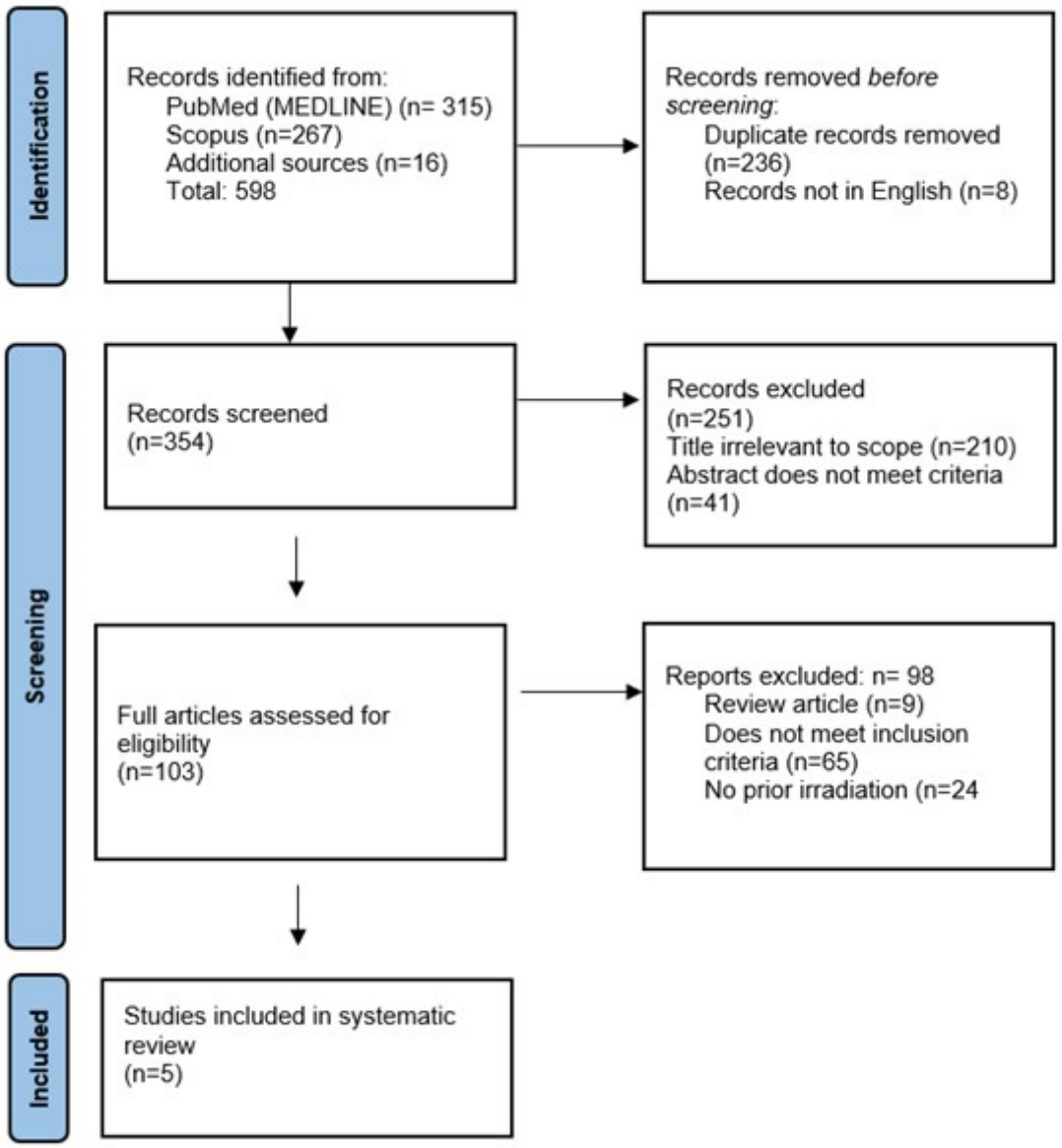

Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. From an initial total of 598 articles, five articles were selected for inclusion into the systematic review.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SBRTtable1bias.docx
- SBRTTable2characteristics.docx
- SBRTTable3Doses.docx
- SBRTtable4outcomes.docx