Comparative oncological and toxicity outcomes of salvage radical prostatectomy versus non-surgical therapies for radio-recurrent prostate cancer: A meta-regression analysis.

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Abstract

Context: Controversy exists as to the optimal salvage modality in radio-recurrent prostate cancer. There is currently an absence of randomised-controlled trials comparing the oncological, toxicity and functional outcomes of salvage radical prostatectomy (SRP), salvage high-intensity focused ultrasound (SHIFU), salvage brachytherapy (SBT) and salvage cryotherapy (SCT).

Objective: To carry out a meta-regression analysis to determine if there is a difference in oncological, toxicity and functional outcomes using data from original publications of salvage modalities in the post-radiation setting.

Evidence acquisition: We performed a critical review of PubMed/Medline citations according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement. We included 63 articles in the analysis; 25 SRP, 8 SHIFU, 16 SCT and 14 SBT.

Evidence synthesis: Median values of the following variables were extracted from each study; patient age, length of follow-up, prostate specific antigen (PSA) before salvage therapy, PSA before radiotherapy, Gleason score before radiotherapy and time interval between radiotherapy and salvage therapy. Functional, toxicity and oncological outcomes were measured according to the rate of impotence, incontinence, fistula formation, urethral strictures and biochemical recurrence. Meta-regression adjusting for confounders found no significant difference in oncological outcomes between SRP and non-surgical salvage modalities. SBT, SCT and SHIFU appear to have better incontinence outcomes compared to SRP. No significant difference in toxicity outcomes between modalities was found.

Conclusions: Oncological outcomes are comparable between SRP and all three non-surgical salvage modalities. We found no significant differences in toxicity outcomes between modalities. SRP however appears to be associated with worse rates of urinary incontinence compared to SBT, SCT and SHIFU.

Patient Summary: We performed a meta-regression analysis to compare oncological, functional and toxicity outcomes between SRP and non-surgical salvage modalities. We conclude that oncological and toxicity outcomes appear to be similar however SBT, SCT and SHIFU are associated with better continence outcomes.

1. Introduction

For more than two decades external-beam radiation therapy (ERBT) and low-dose rate brachytherapy (LDR-BT) have been considered standard practice for the treatment of patients with clinically localised low-risk prostate cancer. Over the years technological advances in this field have seen changes in the delivery of radiotherapy. The integration of various forms of image-guided radiotherapy (IGRT) for ERBT and brachytherapy and delivery with intensity-modulated radiotherapy (IMRT) have enabled accurate dose escalation to improve outcomes and reduce toxicity [1]. Radiobiological models have also indicated that prostate cancer cells are more sensitive to doses delivered in larger fraction sizes than in smaller frequent doses [2]. Our understanding of this has been critical in the introduction and evolution of high-dose-rate brachytherapy (HDR-BT), stereotactic body radiotherapy and proton beam therapy. The introduction of higher radiation doses in addition to the use of adjuvant or neo-adjuvant androgen deprivation therapy (ADT) have both led to improved outcomes leading to the hypothesis that this combination would likely produce

additive improvements [3]. Even in the current era of dose-escalated radiotherapy for prostate cancer and its combination with ADT, biochemical recurrence is not uncommon occurring in approximately 20 to 30% of patients. In a study by Zelefsky et al post-treatment biopsies showed that 15 to 20% of patients treated with dose-escalated radiotherapy have residual disease, suggesting at least a high incidence of local failure [4].

According to European and British urological guidelines, therapeutic options in patients with biochemical recurrence after primary radiation therapy can include salvage radical prostatectomy (SRP), salvage High-Intensity Focused Ultrasound (SHIFU), salvage cryotherapy (SCT) and salvage brachytherapy (SBT). However these guidelines advise that strong recommendations regarding the choice of any of these techniques cannot be made as the available evidence for these treatment options is of very low quality. This is because there are currently no randomised trials to compare the different modalities of salvage treatment in terms of oncological, functional and toxicity outcomes. The majority of available data comes from single- or multi-institutional retrospective or prospective studies with short to intermediate follow-up. SRP appears to be the most popular salvage modality in the post radiation setting based on the number of studies published in the literature. However the decision as to which modality to use is largely based on institutional practice and the availability of a particular technology rather than high quality evidence. Evaluating the relative effectiveness of various salvage treatments in terms of relative cancer control and treatment-related morbidity has proved challenging. This is because of differing treatment-specific definitions of biochemical recurrence, a lack of standardised reporting system of toxicity outcomes and the large heterogeneity

between studies in duration of follow-up, patient demographics, tumour risk profiles in terms of prostate specific antigen (PSA) value and Gleason score as well as the interval between radiotherapy and salvage therapy. To date the only studies attempting to compare these modalities have been systematic reviews [5-7].

To help inform further discussion on this topic we carried out a meta-regression analysis to compare treatment failure rates, functional outcomes and toxicity between the different available salvage options for radio-recurrent disease. Our primary interest was to compare reported outcomes between the most commonly reported salvage modality, SRP and non-surgical modalities.

2. Evidence acquisition

2.1 Search strategy

A systematic review of the literature was conducted using PubMed/Medline electronic databases. The search was restricted to English-Language articles from January 1, 1994 and December 31, 2014. Search terms included ‘prostate cancer recurrence’, ‘prostate salvage therapy’, ‘radio-recurrent prostate cancer’, ‘local salvage treatment’, ‘SRP’, ‘SCT’, ‘SBT’ and ‘SHIFU’. We combined the search terms ‘prostate cancer recurrence’ with ‘SHIFU’ OR ‘SRP’ OR ‘SCT’ OR ‘SBT’ for four separate searches.

2.2 Inclusion criteria

All authors participated in the design of the search strategy and inclusion criteria. Our procedure for evaluating records identified during the literature search followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)

criteria. We included only original articles involving salvage therapy in the post radiation setting. Eligibility criteria for selecting studies included (1) a diagnosis of recurrent prostate cancer after primary radiotherapy (2) studies reporting oncological outcomes in terms of biochemical recurrence rates (3) studies reporting comprehensively on functional and toxicity outcomes in terms of incontinence, impotence, fistula formation and urethral stricture. Any studies commenting on salvage treatments whereby the primary form of therapy was not radiotherapy were excluded from the analysis. The final list of included articles was selected with the consensus of all collaborating authors, verifying that they met the inclusion criteria.

2.3 Data collated

The following data were extracted from each study if available: first author; study size; median age; median follow-up duration; Gleason score prior to primary radiotherapy; median PSA prior to primary radiotherapy; median clinical stage prior to primary radiotherapy; median interval between primary radiotherapy and salvage therapy; administration of adjuvant ADT at the time of primary radiotherapy; median PSA prior to salvage therapy, Gleason score prior to salvage therapy; median clinical stage prior to salvage therapy. Functional outcomes were determined by measuring impotence and incontinence rates and toxicity outcomes evaluated by measuring fistula and urethral stricture formation rates as reported by the individual studies. Oncological outcomes were determined according to biochemical recurrence rate as reported by the individual study. As a pragmatic approach we used each study's predefined criteria for biochemical failure, continence and potency recognizing the lack of consistency of these definitions within and across treatment types.

125 2.4 Data Analysis

126 The outcomes of biochemical recurrence, impotence, incontinence, fistula formation,
127 and urethral strictures were individually compared between salvage therapies using
128 meta-regression analysis with salvage modality included as a moderator. The meta-
129 regression analysis consisted of fitting a logistic mixed effects model to each of the
130 outcome variables using the "rma.glmm" function within the "metafor" package [8] in
131 R software [9] with an explanatory factor variable for salvage modality. For
132 oncological outcome defined as biochemical relapse after salvage, the model adjusted
133 for a further six moderators: age, length of follow-up, PSA before radiotherapy, PSA
134 before salvage therapy, Gleason score before radiotherapy and time interval between
135 radiotherapy and salvage therapy. For both toxicity outcomes and incontinence as a
136 functional outcome the meta-regression model adjusted for age, length of follow-up,
137 PSA before salvage therapy, and PSA before radiotherapy and Gleason score before
138 radiotherapy. Unfortunately no covariate adjustment was possible for impotence. The
139 reason behind this modeling strategy was that many studies had missing data on the
140 moderators, which reduced the dataset available for analysis and hence caused
141 problems with model fitting. We always aimed to include the maximum number of
142 moderators possible in each analysis, and this meant that the analyses for some
143 outcomes included more moderators than for others.
144

145 The reported median was used to summarise the aforementioned moderators; except
146 when missing, in which case the mean was used instead where available. A value of
147 "0.5" was added to any zero frequencies prior to analysis. The amount of residual
148 heterogeneity between studies was assessed by reporting the absolute value of τ^2
149 (between-study variance) and the I^2-statistic. Summary effect size differences in

outcomes between the different surgical modalities were expressed as odds ratios (OR) with 99% confidence intervals and p-values. Due to the high number of models and outcome variables considered in multiple testing, a 1% significance threshold was used to determine statistical significance. To investigate publication bias, funnel plots were constructed of sample size against model residuals calculated via linear meta-regression models of logit-transformed proportions, with salvage therapy included as the only moderator.

3. Evidence synthesis

The literature search yielded 975 papers. These were then individually screened for their suitability for inclusion in this study. 912 articles were excluded from the study resulting in 63 articles [10-71] being finally included in the analysis (Figure 1). One of the SCT studies included 2 separate cohorts of patients who underwent SCT, the outcomes of which we considered separately [45] therefore a total of 64 studies were included in the analysis. 25 for SRP; eight SHIFU, 17 SCT and 14 SBT. Five of the studies provided no data on mean or median age, and three did not record the duration of follow-up. 30 studies had no data on PSA prior to primary radiotherapy and seven papers had no data on PSA prior to salvage therapy. In addition, 33 of the studies did not mention the Gleason Score prior to initial radiotherapy and 22 studies provided no data on the interval between radiotherapy and salvage therapy. The total number of patients was 4564 with a median study size of 40 (range 4-404). Further base line characteristics of the original publications identified by the literature search are shown in table 1. A funnel plot of the model residuals against sample size showed no clear evidence of publication bias for biochemical recurrence as an outcome variable (Figure 2). However there were some limited indications of publication bias when considering toxicity and functional outcomes particularly that of incontinence.

The cohort size of each study and the overall percentage relapse rate at any time as well as toxicity and functional outcomes are represented as bubble plots (Figure 3). Overall SCT included the largest population sizes (110 subjects on average) while the SBT studies included the smallest number of patients (26 subjects on average). Weighted summary statistics for age, length of follow up, PSA before salvage therapy, PSA before radiotherapy Gleason score before radiotherapy, interval between radiotherapy and salvage therapy and oncological, toxicity and functional outcomes for each salvage modality is displayed in Table 2.

3.1 Meta-regression analysis for biochemical relapse

The bubble plot for biochemical recurrence showed no obvious visual difference between the salvage modalities (Figure 2) and this was confirmed in the meta-regression analyses. Two analyses were done for biochemical recurrence. The first adjusted for no additional moderators (Model 1) and included 61 studies. This analysis showed no significant difference in biochemical relapse between SRP and the non-surgical salvage modalities (**SBT relative to SRP** OR 0.98 99%CI 0.493-1.95, p=0.939, **SCT relative to SRP** OR 1.49 99%CI 0.816-2.73, p=0.087, **SHIFU relative to SRP** OR 1.17 99% CI 0.537-2.56, p=0.60). A further analysis to compare the oncological outcomes between the non-surgical salvage modalities revealed no significant difference in biochemical recurrence either (**SBT relative to SHIFU** OR 0.836 99%CI 0.355-1.97, p=0.590, **SCT relative to SHIFU** OR 1.27 99%CI 0.577-2.81, p=0.430, and **SBT relative to SCT** OR 0.656 99%CI 0.326-1.32, p=0.121).

The second analyses adjusted for the following variables: age, PSA before radiotherapy and salvage therapy, Gleason score before radiotherapy, follow-up

duration and interval between radiotherapy and salvage therapy (Model 3). After accounting for the above variables 18 studies were eligible for the second analysis. The residual heterogeneity between studies for this analysis was estimated to be zero. The meta-regression analysis following adjustment for these variables again showed no significant difference in biochemical recurrence rates between the SRP and the other non-surgical salvage modalities (**SBT relative to SRP** OR 0.623 99% CI 0.237-1.64, p=0.207, **SCT relative to SRP** OR 0.98 99%CI 0.294-3.27, p=0.966, **SHIFU relative to SRP** OR 1.32 99% CI 0.419-4.16, p=0.533. Subsequent analysis of the non-surgical salvage modalities did not find one superior to the other in this respect either (Table 3). These results are consistent with systematic reviews on the topic where no difference in oncological outcomes between the different salvage modalities is demonstrated.

3.2 Meta-regression analysis for toxicity outcomes

The bubble plots for urethral stricture and fistula formation showed no visual difference between the four salvage modalities (Figure 2). For both urethral stricture and fistula formation two meta-regression analyses were done. The first adjusted for no additional moderators and included 37 and 30 studies for fistula and urethral stricture respectively. In this first analysis no significant difference was demonstrated between SRP and the non-surgical salvage modalities in the rate of fistula formation (Table 3). In addition the first meta-regression analysis demonstrated no significant difference in the rate of urethral stricture formation between SRP and the non-surgical salvage modalities (**SBT relative to SRP** OR 0.603 99%CI 0.128-2.85, p=0.402, **SCT relative to SRP** OR 0.219 99%CI 0.0309-1.56, p=0.046, **SHIFU relative to**

SRP OR 0.884 99% 0.293-2.67, p=0.775). The second meta-regression adjusted for age, length of follow-up, PSA before radiotherapy, PSA before salvage therapy and Gleason score before radiotherapy for both toxicity outcomes. A total of 18 studies and 14 studies were eligible for inclusion in the second analysis for fistula and urethral strictures respectively. The residual heterogeneity between studies for both analyses was estimated to be zero. Following adjustment for these variables the analysis again found no significant difference in the rates of urethral strictures and fistula between SRP and all the non-surgical salvage modalities across the meta-regression analysis. A further analysis focusing only on comparing non-surgical modalities for both these outcomes similarly found no significant differences (Table 3). These results suggest that none of the salvage options appear to have an advantage in the context of a reduced risk of complications.

3.3 Meta-regression analyses for functional outcomes

The bubble plot for incontinence demonstrated an apparent benefit of all three non-surgical salvage modalities compared to SRP when considering the rate of incontinence. This was particularly the case for SBT and SCT and less so for SHIFU. (Figure 2).

For incontinence two meta-regression analyses were undertaken. The first adjusted for no additional moderators and included a total of 49 studies. In this analysis SBT and SCT had significantly better outcomes in terms of incontinence compared to SRP. However in this analysis SHIFU did not demonstrate significantly better incontinence outcomes compared to SRP at the $p<0.01$ level of significance (Table 3). A further analysis between the non-surgical salvage modalities found that SBT and SCT had

247 significantly better incontinence outcomes compared to SHIFU, however there was no
248 significant difference when comparing SCT to SBT (**SBT relative to SHIFU** OR
249 0.184 99%CI 0.0445-0.761, p=0.002, **SCT relative to SHIFU** OR 0.233 99%CI
250 0.0727-0.749, p=0.001, **SBT relative to SCT** OR 0.789 99%CI 0.211-2.95, p=0.644)

251 The second analysis adjusted for age, length of follow-up, PSA before radiotherapy,
252 PSA before salvage therapy, and Gleason score before radiotherapy. A total of 18
253 studies were eligible for inclusion in this analysis. The residual heterogeneity was
254 calculated to be 65.67% implying that substantial between-chort differences remain
255 even after taking into account surgical modality and other factors.. Following
256 adjustment for these variables there was evidence that all three non-surgical salvage
257 modalities were significantly superior to SRP in terms of incontinence outcomes
258 (**SBT relative to SRP** OR 0.00595 99%CI 0.000245-0.144, p<0.001, **SCT relative to**
259 **SRP** 0.0142 99%CI 0.00209-0.0965, p<0.001 **SHIFU relative to SRP** OR 0.0822
260 99%CI 0.00868-0.778,p=0.004). When considering the non-surgical salvage
261 modalities alone SCT was found to be superior to SHIFU. In contrast to the first
262 analysis there was insufficient evidence that SBT has improved incontinence
263 outcomes compared to SHIFU (table 3) These results suggest that of all modalities,
264 SRP appears to have the highest risks of urinary incontinence. A caveat to this is the
265 high residual heterogeneity in our analysis.

266 Impotence outcomes were the poorest recorded parameter and are therefore the least
267 reliable in our study. The bubble plots for impotence demonstrated an apparent
268 benefit of SCT over SRP however due to the limited available data on impotence
269 outcomes an adjusted meta-regression model was not possible. Furthermore SHIFU
270 was not included in this analysis as only one of the included studies on SHIFU
271 reported impotence outcomes; therefore only SRP, SCT and SBT were considered in

the statistical analysis. A total of 19 studies were included in the analysis. The residual heterogeneity was calculated to be 92.64%, which is very high and suggests that substantial between-study differences in reported impotence rates remain even after taking into account surgical modality. The only finding was that SCT might have superior outcomes in terms of impotence compared to SRP. There was no other significant difference found between modalities; although as stated above, we were unable to compare SHIFU with the other modalities (**SBT relative to SRP** OR 0.581 99%CI 0.0162-20.9, p=0.664, **SCT relative to SRP** OR 0.0567 99%CI 0.00428-0.751, p=0.005, **SBT relative to SCT** OR 10.3 99%CI 0.217-484, p=0.097).

3.4 Discussion

SRP is currently the most widely reported salvage modality in the literature and there has been a resurgence in its popularity with the introduction of robotic assisted prostatectomy [72]. More recently the advent of new minimally invasive modalities and the concept of focal therapy has also been increasingly applied in the salvage therapy context [73,74]. There is however currently no consensus as to which salvage modality should be used or is optimal for radio-recurrent disease. Our meta-regression analysis of the current available literature showed no significant difference in oncological outcomes between SRP and the other three non-surgical salvage modalities. Also further analyses between the non-surgical salvage modalities did not find one more superior to the other in this respect. With regard to toxicity outcomes our results suggest that there is again no significant difference in the rate of fistula and urethral stricture formation between SRP and the other non-surgical salvage modalities. SRP however was associated with a greater rate of incontinence in

296 comparison to all three non-surgical salvage modalities. Of note, despite correction
297 for variables potentially associated with incontinence outcomes we still identified a
298 degree of residual heterogeneity in the results. This coupled with the possibility of
299 publication bias as demonstrated by the funnel plots urges us to interpret our results
300 with some caution. Nevertheless, our analysis of incontinence outcomes agree with a
301 systematic review by Parekh et al who noted that incontinence rates were highest
302 among SRP patients with a rate of 49.7% across series [6]. Publication bias and
303 heterogeneity was also identified in our analysis of potency outcomes primarily due to
304 the limited data reporting. As a result we are unable to draw any robust conclusions as
305 of a superior modality with regards this outcome..

306 This study has a number of inherent limitations. Data was extracted from published
307 manuscripts, rather than from original patient data, so a degree of reporting bias is
308 inevitable. Not all studies reported patient age, length of follow-up, PSA before
309 salvage therapy, PSA before radiotherapy, and Gleason score before radiotherapy, and
310 time between radiotherapy and salvage therapy, which meant that missing data was
311 extensive and the data available for analysis was often limited. For every outcome we
312 therefore attempted to adjust for as many confounders possible in the final meta-
313 regression model. As mentioned, our assessment of residual heterogeneity indicates
314 that for incontinence and impotence outcomes there remains a significant amount of
315 unexplained variability in the data that we have not been able to account for. We also
316 note the relative short follow-up duration of studies reporting outcomes for SCT, SBT
317 and SHIFU compared to SRP. Studies with longer follow-up duration will be
318 necessary to accurately compare SRP with the non-surgical salvage modalities.
319 Finally the interpretation of biochemical failure in our study depended on the
320 definition used by individual published series and was based on a pragmatic approach

due to the diverse interpretation of relapse between the salvage modalities. Nevertheless despite these limitations our conclusions are in strong agreement with the findings of recently published systematic reviews, which have found no significant differences in oncological outcomes between the salvage modalities but suggest that SRP may have worse functional outcomes particularly in the rates of incontinence.

4. Conclusion

This study is unique in that it endeavoured to adjust for heterogeneity prior to statistical analysis and is the first to use a meta-regression model to compare salvage modalities. Our findings in this study reinforce conclusions from systematic reviews suggesting that current salvage modalities appear to have similar oncological and toxicity outcomes. In particular, SRP does not appear to confer any added benefit in terms of disease control compared to more minimally invasive approaches but instead may potentially increase functional debility. The wide variation in study parameters, outcome measures and endpoints reinforce the urgent need for prospective randomised controlled studies directly comparing between modalities as well as standardised definitions of outcomes and longer follow-up times. Until then we hope our data and findings will help inform clinicians and patients when deciding between different salvage therapy options.

List of abbreviations: SRP; salvage radical prostatectomy, SHIFU; salvage high-intensity focused ultrasound, SBT; salvage brachytherapy, SCT; salvage cryotherapy, ERBT; External Beam Radiation Therapy, LDR-BT; Low-Dose Rate Brachytherapy, IGRT; Image-Guided Radiotherapy, IMRT; Intensity-Modulated Radiotherapy, HDR-BT; High-Dose-Rate Brachytherapy, ADT; Androgen Deprivation Therapy, PSA; prostate specific antigen, PRISMA; Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria.

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