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Decision regret in patients with localised prostate cancer: a systematic review and meta-analysis

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Abstract

Context

Treatment choice for localised prostate cancer remains a significant challenge for patients and clinicians with uncertainty over decisions potentially leading to conflict and regret. There is a need to further understand prevalence and prognostic factors of decision regret to improve patient quality of life.

Objective

To generate best estimates for the prevalence of significant decision regret localised prostate cancer patients. Secondly, to investigate prognostic patient, oncological and treatment factors associated with regret.

Evidence acquisition

We performed a systematic search of MEDLINE, Embase, and PsychINFO databases including studies evaluating either prevalence or patient, treatment, or oncological prognostic factors in localised prostate cancer patients. Pooled prevalence of significant regret was calculated with formal prognostic factor evaluation conducted per factor identified.

Evidence synthesis

Significant decision regret was present in a pooled 19.58% (95% CI 15.94-23.37) of patients across 14 studies and 17883 patients. This was lower in active surveillance (12.86%) with little difference between those who underwent radiotherapy (18.89%) or prostatectomy (17.94%). Evaluating individual prognostic factors demonstrated higher regret in those with poorer post-treatment bowel, sexual and urinary function, decreased involvement in the decision-making process and black ethnicity. Although, evidence remains conflicting, with low or moderate certainty of findings.

Conclusions

A significant proportion of men experience decision regret after a localised prostate cancer diagnosis. Monitoring those with increased functional symptoms and improving patient involvement in the decision-making process through education and decision aids may reduce regret.

Patient summary

We looked at how common regret in treatment decisions is after treatment for early-stage prostate cancer and factors linked with this. We found that one in five regret their decision with those who had experienced side effects or were less involved in the decision-making process more likely to have regret. By addressing these clinicians could reduce regret and improve quality of life.

Introduction

Prostate cancer (PCa) is the second most common cancer diagnosis received by men worldwide[1]. After diagnosis, men face a huge array of treatment choices for localised PCa ranging from non-interventional active surveillance (AS) to major curative treatments such as radical prostatectomy (RP) or external beam radiotherapy (EBRT). Curative treatments offer similar survival rates but can have a significant impact on a patient's quality of life (QoL) and mental health as a result of their urinary, sexual and bowel related side effects (SE)[2–7]. Conversely, those considering AS must weigh up the short term gain of reduced SE profile versus the potential for future disease progression[8,9].

Given these options, selecting the best treatment choice for localised PCa can pose a significant challenge and cause uncertainty amongst patients and physicians and lead to decisional conflict and regret[10]. Regret can be conceptualized as an aversive emotion experienced when we imagine a current situation that would be more favourable if different decisions had been made [11,12]. When justifying a decision, patients conduct a comparative evaluation of potential outcomes and this can trigger the emotion of self-blame if they perceive to have made the wrong choice[12]. A patient experiencing decisional regret (DR) may suggest an error in the process through which the treatment option was chosen[13]. Increasing patient involvement in decision making can hypothetically reduce subsequent regret by improving the justifiability of the process and improve a patient's certainty of choice[14].

Given the complexity around treatment choices and regret, there is a need to better understand DR, particularly due to its impact on QoL [10,15]. This could improve patient counselling, ensure appropriate monitoring of at-risk groups and help to design effective pre- and post-treatment interventions.

Therefore, the aims of this review were to:

1. Generate a best estimate for the prevalence of significant DR and its severity in the context of treatment for localised PCa

2. Investigate prognostic patient, oncological and treatment factors associated with subsequent DR

Evidence Acquisition

The reporting of our review was conducted in line with PRISMA and extended PRISMA-S guidelines[16,17]. For evaluation of DR prognostic factors the PROGRESS framework and review guidance was followed[18]. Where meta-analysis was not possible due to heterogeneity the synthesis without meta-analysis (SWiM) reporting guidelines were utilised[19]. A prior protocol was published on the PROSPERO database (CRD42021279843).

Study eligibility criteria

Studies included in this review were observational and interventional (randomised and non-randomised). Longitudinal and cross-sectional observational studies were included with both prospective and retrospective designs. Studies must have evaluated patients with an initial diagnosis of clinically localised PCa (T1a-T2c)[20]. Where multiple stages of disease were evaluated extractable data for patients with localised PCa was required for inclusion. There was no further limitation to patient cohorts included in terms of demographics, clinical characteristics or treatments undergone. Lastly, for inclusion studies must have used a validated tool to measure DR, such as the decision regret scale (DRS) with a pre-determined cut off point or definition for caseness[21]. Adapted from work by Clark et al [15,22], the DRS was validated by Brehaut et al [23].

Information sources and search strategy

Multiple databases were searched for potentially relevant records. These included Cochrane library, MEDLINE (via PubMed), Embase (via OvidSP) and PsycINFO (via OvidSP) from inception to 13/9/2021. Grey literature was searched through abstracts on Embase and ongoing studies via the WHO international clinical trials registry platform (ICTRP). Authors of potentially useful studies were contacted for any preliminary data. Lastly, a manual reference review of included articles and identified reviews was conducted. The search strategy was piloted prior to use and included a mixture of key words and MeSH terms with the full search strategy available in supplementary material 1.

Study selection process

Study selection was conducted utilising Rayyan software[24]. After deduplication each individual study was independently screened by two authors (a combination of JF, VC, AA and AN) against the inclusion criteria. Any discrepancies were discussed until 100% agreement with a fifth reviewer (OB) acting as adjudicator.

Data collection process and data items

Data extraction of each included article was conducted by two independent reviewers (a combination of JF, VC, AA and AN) onto a pre-defined and piloted extraction sheet. Study level data extracted included study type and methodology, inclusion and exclusion criteria, patient demographics and treatments received and tool/cut off used to define DR. Where data was available for multiple time points data was extracted for all. However, in these cases for prevalence evaluation data furthest from diagnosis was utilised. Primary outcome measures extracted included number of patients with and without DR and calculated prevalence. Furthermore, for the second study aim, each predictor of DR was established using odds ratios, hazard ratios, correlation coefficients or means differences, and whether the analysis was multivariate or univariate. For this secondary aim the CHARMS-PF checklist was used to guide the development of the extraction sheet.

Summary measures and statistical analysis

A meta-analysis was conducted for both study aims where homogenous study methods were utilised, and outcome data was available in ≥3 studies. For prognostic factor evaluation this required data availability for an individual factor utilising the same assessment method and uniformly utilised either multivariate or univariate analysis. For pooled prevalence calculations the 'Metaprop' function was utilised[25]. A random effect analysis was conducted due to heterogeneity, using Freeman-Tukey Double Arcsine Transformation to stabilise variances. Proportions were converted to percentages and

presented with a 95% confidence interval. For prognostic factor evaluation pooled ORs were calculated using the restricted maximum likelihood approach. For all analyses Stata 16 software was utilised.

A stratified sensitivity analysis for the pooled prevalences was conducted by excluding studies identified as high Risk of Bias (RofB), through assessing study size, design, location and through the diagnostic criteria utilised.

Unfortunately, for multiple prognostic factors meta-analysis was infeasible due to high variance in assessment methods used for the individual prognostic factors. For these a structured qualitative synthesis was performed. Studies were grouped by prognostic factor with vote counting utilised to establish the number of significant studies and direction of effect with RofB rating and size of effect then used to measure the significance of each finding.

Study risk of bias and certainty of evidence

Individual study quality was conducted independently by two reviewers (a combination of JF, VC, AA and AN). For the primary research question the Hoy RofB tool was utilised [26]. For the secondary research question the Quality in Prognostics Studies (QUIPS) tool was used[27]. Studies were not excluded on a basis of a high RofB; however, they were utilised within a sensitivity analysis for exploration of heterogeneity. Evaluation of the overall certainty of evidence was conducted for our secondary aim, using the GRADE approach for prognosis on a per outcome basis if evaluated by two or more studies [28].

Evidence Synthesis

Results

Study selection and characteristics

3268 articles were screened for inclusion with 3085 excluded via title, abstract and full text screening. A final 33 studies were subsequently included combining a total of 23,208 patients (Figure 1). The included studies were conducted in the following countries; Eighteen from the United States of America, four from Germany, three from the United Kingdom, two from the Netherlands, two from Canada and one from each of Taiwan, Australia and Italy. Further characteristics of the included studies are outlined in Supplementary Table 1.

Prevalence and Severity

A meta-analysis of fourteen studies, and 17883 patients, identified significant DR in a pooled 19.58% (95% CI 15.94-23.37) of patients (Figure 2)[29–43]. When dividing this by individual treatment cohorts, we found significant DR in 12.86% (95% CI 6.78-20.43) in those undergoing AS (Figure 3a), 16.08% (95% CI 8.54-25.25) post focal therapy (Figure 3b), 18.89% (95% CI 12.18-26.63) for RT (Figure 3c), and 17.94% (95% CI 14.56-21.59) after RP (Figure 3d). Overall a significant proportion of total variability was due to between-study heterogeneity (I^2=92.48%) with a sensitivity analysis (Supplementary Figure 1), demonstrating study size to be one potential factor in this, with medium and large studies evidencing higher rates of DR (p=0.024). Similarly, study design and number of centres were significant with cross sectional studies reported higher rates of DR compared with cohort (p<0.01), and multicentre studies reporting higher DR (p=0.05). However, continent (p=0.23), tool used to assess DR (p=0.21) and treatments evaluated (p=0.79) were non-significant. As Supplementary Figure 2 demonstrates the severity of DR varied greatly (range of mean scores 4.17-44.74, median = 10.1, IQR 13.6-16.8)[30,38,39,44–54]. Visual inspection of a funnel plot and Egger's tests (p=0.55) demonstrated no significant publication bias for overall prevalence (Supplemental Figure 5).

Prognostic factors

Patient factors

Demographic factors

Twelve studies reported on the effect of age on DR[33,34,36–38,46,48,49,52,54]. Measured as multivariate continuous variable, age at treatment was not significantly associated with DR on pooling of results across four studies and 3005 patients (OR 0.98, 95% CI 0.92 – 1.05) (Supplementary Figure 3). Narrative synthesis of the remaining studies identified no association between age and DR in any study with high certainty of evidence[33,38,49,52].

Eight studies reported the differences in DR in patients of various ethnicities[33,34,34,37,39,42,46,54]. A pooled analysis of 3102 patients across three studies found that black men were not at significantly higher odds of experiencing DR as compared to other ethnicities (multivariate; OR 1.56 95% CI 0.84 – 2.88), (Supplementary Figure 4). However, a further three studies found black men were more likely to experience DR compared with Caucasian men with low certainty of evidence[39,46], with one finding no association[33]. Two further studies also found no significant difference in DR when comparing Caucasian patients with patients of Hispanic or other origins[29,33], albeit one found an association between Hispanic ethnicity and regret[46].

A total of ten studies totalling 5976 patients investigated the relationship between education level and DR[31–34,36,37,46,49,52,53]. However, pooling for results was not possible due to varying classifications used. Of these, two studies reported increased risk of DR for patients with lower education attainment with low certainty of evidence[32,37]. Three studies investigated the relationship between employment status and DR and no significant association was reported with low certainty of evidence[31,53,55]. No association between comorbidities DR was evidenced by two studies[29,33].

Quality of Life Outcomes

QoL outcomes were the most evaluated prognostic factor with a total of 13 studies and 7377 patients evaluating at least one[29–33,36,37,39,44,48,54,55]. However, few utilised similar outcome measures or analysis

methods meaning pooling was not possible. A total of 11 studies reported the effects of sexual function on DR. Eight studies reported odds ratios from logistic regression [30,32,34–37,40,41]. Seven reported significantly more DR in patients with worsened sexual function with moderate certainty of evidence, the corresponding evaluation tool and odd ratios are outlined in Supplementary Table 2. Two studies reported associations between lower SHIM scores and DR[29,39].

A total of twelve studies reported the relationship between either urinary incontinence (4730 patients)[29,31,32,37,39,44,48,54], or urinary irritation (4540 patients)[29,31–33,37,44,49,55,56], on DR. Four reported a statistically significant association between urinary incontinence and DR with moderate certainty of evidence, however, a further four studies reporting no correlation (Supplementary Table 3). Four reported a statistically significant association between worse urinary symptoms (irritative +/- obstructive) and DR with moderate certainty of evidence, and a further five studies reporting no correlation (Supplementary Table 4). Six studies including 4204 analysed the relationship between DR and bowel function (Supplementary Table 5)[29,32,33,36,37,44]. Three reported a significant correlation between worse bowel function and DR with low certainty of evidence[32,33,36]. A total of three studies including 2612 patients analysed the relationship between hormonal side effects and DR[29,32,37]. Two found a correlation between increased symptomatology and DR with moderate certainty of evidence[29,32]. The relationship between overall QoL and DR was reported by two studies and neither found a correlation[29,44].

Oncological Factors

Five studies totalling 2309 patients reported the association between clinical stage and DR using a variety of categorical variables negating the possibility of pooling [29,32,33,36,39]. A single study reported lower DR in those with earlier stage disease with low certainty of evidence[32]. The association between risk profile and DR was assessed in three studies[29,3334], and no association was found with high certainty of evidence. Increased PSA on diagnosis was not associated with increased DR across three

studies with high certainty of evidence[29,33,36]. Four studies explored the relationship between initial Gleason score and DR and no association was found with low certainty of evidence[29,33,39,46].

Treatment Factors

Decision making process and perceptions of treatment

Six studies including 2086 patients analysed a patient's role in the decision-making process with four reporting an active role reduced DR with low certainty of evidence [34,36,37,4849,53]. Two studies analysed the role of patient's perception of their treatment and the correlation with DR with both evidencing worse DR in patients reporting less satisfaction with outcomes[37,44]. Three studies analysed patient knowledge and informed decision making with two reporting reduced DR in those with improved knowledge however there was very low certainty of evidence [31,36,57].

Treatment choice and outcomes

Overall seven studies including 4642 patients evaluated the role of treatment received on subsequent DR[32,33,36,37,50,55]. However, few compared similar cohorts or analysis methods meaning no pooling of results was possible as displayed by vote counting in Table 1. Six studies including 2621 patients analysed the relationship between treatment success and lower DR [31,33,38,39,48,52], with only three of the six studies evidencing a significant correlation with low certainty of evidence [31,38,48].

Risk of bias assessment

Studies evaluating significant DR prevalence were of overall low risk bias with a median score of nine across the ten assessed domains. Only one study out of thirteen meta-analysed for prevalence was judged to be at high RofB overall with none of the fourteen studies used solely for severity scores found to be at high RofB (Supplementary Figure 6). The most identified concerns were that of non-response bias and a lack of random sampling or census. QUIPS was utilised for twenty-two prognostic factor studies (Supplementary Figure 7), with only three studies were assessed to be at low RofB

across all six assessed domains. The domain most at risk was study attrition with sixteen studies found to be at moderate RofB.

Discussion

The primary aim of this review was to provide a summary of existing evidence on the prevalence of DR in localised PCa. Evidencing that nearly one in five patients regret their treatment decision is substantial and suggests major revisions to decision making pathways are needed**.** These rates are greater than in other cancers including breast [58], and thyroid[59]. This may reflect the array of treatment options available in PCa and their significant associated side effects. Furthermore, PCa treatment have a significant impact on men's body image and masculinity[60], and as DR was associated with perceived diminished masculinity in this review this may explain higher DR versus less emasculating treatments. Whilst lower than other treatment modalities, the findings of one in eight men undergoing AS regret their decision may relate to findings suggesting patient's that choose AS have greater PCa related anxiety and less certainty of treatment choice[61]. The decision to enrol in AS leaves some men feeling as if they are living with untreated cancer[62], and can lead to significant levels of anxiety[63].

The secondary aim of this review was to outline the existing evidence on prognostic factors impacting DR in localised prostate cancer. Black men with localised PCa may be more likely to experience DR although the evidence is conflicting. Previous findings demonstrate Black men are more likely to experience medical mistrust and masculinity concerns which are independent predictors of DR[54]. The included studies suggested there was no relationship between age and DR this may be related to the increased likelihood of sexual and urinary functional recovery by younger men mitigating regret compared with older patients who may have already experienced some aspects of functional decline[64,65]. Our findings also suggest increased knowledge of PCa and treatment options and involvement in the decision-making process can reduce DR. Previous reviews in cancer patients echo these findings with regret more common in those receiving incomplete information regarding their diagnosis, too many treatment options or having low understanding of side effects[66]. This relationship may be more nuanced with equating a patient's preferred role with their actualised role in the decision of key importance[67]. Lastly, findings highlighting the importance of functional outcomes in predicting DR reflect the significant impact these can have on a patient's QoL.

The current literature displays multiple areas of weakness. Several studies assessed DR at one year or less post treatment which might have artificially inflated DR due to worsened side effect profiles that may have ameliorated with time. The use of different cut offs to define DR may contribute to outcome misclassification bias as shown by high variation in prevalence. Many papers reported associations with DR and various QoL measurements however due to a variety of scales and categorisation of prognostic variables used meta-analysis was infeasible. In future the use of continuous variables and consistent use of validated tools would allow improved synthesis. While quality assessment found studies to generally be at low RofB two key areas were not. Several papers did not report on the characteristics of suitable patients not included in the study or who dropped out. Furthermore, several studies of prognostic factors failed to identify, and mitigate for, potential confounding variables.

Certainty of evidence across outcomes was generally moderate or low with inconsistency and imprecision the major sources of downgrading (Supplementary Tables 6-9). The findings of this review expose specific areas for future research. Particularly, this should include the role in decision making, ethnicity, QoL outcomes such as sexual and urinary function, treatment received, and approach of treatment undergone such as different delivery methods for radiotherapy or surgical approaches for radical prostatectomy. This must include appropriate protocol supported and sized prospective studies assessing DR at multiple time points conducted in line with the Prognostic Research Strategy (PROGRESS) guidelines[68]. The lack of research focussing on the relationship between pre- and post-treatment mental health and the correlation of these with DR should be addressed, especially given the potential link between DR and anxiety and depression post treatment[66]. Furthermore, research to identify the role of a patient's preferred and actualised role in the shared decision-making process and how the equation of these impacts decisional conflict and regret would be of key importance to improve decision aids (DA).

A recent metanalysis[69], found that DAs for localised PCa had no significant impact on treatment DR. A systematic review of RCTs[70], found that improving shared decision making increased patient knowledge of PCa and treatment options but did not significantly reduce DR[66]. Whilst our review

suggests that greater patient involvement in decision making, and improved patient knowledge were associated with lower DR the evidence was conflicting and of low certainty. A systematic review of DA in minority patients conducted by Nathan et al[71], found that culturally tailored DAs were more impactful. These findings suggest the need to establish a better understanding of why patients choose different treatments and allow for tailored DAs to be developed and flexible shared decision-making discussions to take place. The use of pre-treatment questionnaires, such as the PCa Beliefs Questionnaire, may facilitate matching a patient's preferred and realised role in the decision-making process. Preventing and ameliorating DR through an improved adaptable decision-making process, ensuring patients understand the treatment's differing side effect profiles and improved aftercare to increase functional recovery is crucial. However, given the high prevalence of DR across the treatment groups the need to raise this difficult topic with patients after treatment is likely to remain. Whilst no research exists on how best to approach this discussion including the DRS in pre-consultation questionnaires at follow up may facilitate an exploration of reasons for DR, if identified, so the clinician can provide appropriate support to mitigate these. Although cancer related anxiety in AS patients does seem to reduce over time[63], improving access to schemes that reduce this such as exercise[72], fostering support and coping strategies for patients and their families[73], and psychotherapeutic interventions[74], may also mitigate DR. The established link between side effects such as sexual, bowel and urinary dysfunction reemphasises the importance of outlining this pre-treatment and identifying and treating them when they arise to reduce DR. This is especially important in post RP patients where the prompt treatment of side effects should be a key facet of a patient's management plan[75], furthermore comprehensive pre-operative counselling focussing on sexual side effects and outlining realistic recovery timescales mitigate DR[38]. Similarly, for patients undergoing RT identification and treatment of side effects such as phosphodiesterase inhibitors for erectile dysfunction[76], and alpha blockers or anticholinergics for irritative urinary symptoms may ameliorate DR[77].

Potential limitations of this SR and MA include the possibility of missing pertinent studies, although we attempted to reduce this risk through a comprehensive search strategy. Furthermore, the

heterogeneity of studied prognostic factors in both choice and assessment meant meta-analysis was rarely appropriate. Though RofB across the studies was generally low the use of a wide variety of time points and cut offs for caseness introduced significant heterogeneity as shown by the sensitivity analysis.

Conclusion

A significant proportion of men experience DR after treatment for localised PCa suggesting a need to adapt the decision-making process and mitigate the causes of DR. This was most common after curative treatment in the form of RP or RT, which may be explained by the apparent prognostic role of functional outcomes in developing DR. The strong association between side effects and DR suggest prompt identification and treatment of these are crucial to mitigate DR. Lastly, increasing patient involvement in the decision-making process, in line with their preferred role, through education and DAs, may reduce DR.

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