INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Stereotactic Radiation therapy in early and locally advanced inoperable renal cell carcinoma: treatment outcomes, patterns of failure and risk factors

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Review question / Objective: **The patterns of failure post-treatment were mainly classified into three categories: local recurrence (LR), and regional and distant metastasis (DM). LR was defined as the first recurrence of the disease histology type at the primary tumor site. Regional recurrence is the recurrence of inguinal and/or retroperitoneal lymph nodes. DM was defined as a recurrent disease at a distant site.**
To identify high-risk factors for recurrences post-treatment, which may help clinicians in identifying poor prognostic factors.
Eligibility criteria: **Adult patients (≥18 years) diagnosed with early or locally advanced renal cell carcinoma deemed medically inoperable will be assessed in the review.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 March 2023 and was last updated on 23 March 2023 (registration number INPLASY202330083).

INTRODUCTION

Review question / Objective: **The patterns of failure post-treatment were mainly classified into three categories: local recurrence (LR), and regional and distant metastasis (DM). LR was defined as the first recurrence of the disease histology type at the primary tumor site. Regional recurrence is the recurrence of inguinal and/or retroperitoneal lymph nodes. DM was defined as a recurrent disease at a distant site.**
To identify high-risk factors for recurrences post-treatment, which may help clinicians in identifying poor prognostic factors.

Condition being studied: Renal cell carcinomas (RCC) are the most common histologic type constituting 80-85% of all kidney neoplasms and they are further subdivided into the clear cell (80-85%), papillary (10-15%) chromophobe (5-10%), and oncocytoma (<5%) types. RCC is among the most radioresistant tumors, however, ablative radiation therapy with higher doses has shown a good response in terms of tumor eradication leading to improved outcomes with a high local control rate in primary and metastatic renal cell cancer. With the increased utilization of diagnostic imaging modalities, the incidence of renal cell carcinoma (RCC) has seen a rise, especially in the elderly population and surgical resection forms the mainstay of treatment. However, the increased age is associated with increased medical comorbidities including diabetes, hypertension, and cardiovascular diseases, deeming surgery not possible in such cases.

Active surveillance with delayed interventions does not seem a viable option as larger tumor size confers poor prognosis with decreased cancer-specific survival by 15%. Thermal ablation with either cryoablation or radiofrequency ablation (RFA) is associated with limited local control benefit and associated with increased complications. Stereotactic body radiation treatment (SBRT) has helped overcome the radioresistance associated with RCC with favorable immune response leading to significant tumor regression. SBRT is a non-invasive treatment modality and offers the advantage of outpatient-based treatment which is extremely useful for patient logistics, especially in the medically inoperable subgroup. However, we still lack clarity regarding the radiation doses delivered as well as the associated long-term toxicity profiles in patients treated with SBRT. In addition, there have been advances in the treatment delivery modalities and the contouring of various organs at risk which would further impact the outcomes and reduce treatment-related toxicities.

The results from the International Radiosurgery Oncology Consortium for Kidney (IROCK) have been encouraging in showing good efficacy and tolerability with a modest impact on renal function with SBRT as a viable treatment option for medically inoperable RCC. The current National Comprehensive Cancer Network guidelines 2022 version 2 state that SBRT can be considered for medically inoperable stage I kidney cancer (Category 2B) and stage II/III kidney cancer (Category 3) (15). Similarly, the European Association of Urology and the European Society of Medical Oncology have proposed SBRT as an alternative treatment modality in inoperable localized RCC.

There have been previous systematic reviews and meta-analyses assessing the feasibility and safety of SBRT in medically inoperable renal cell carcinoma, but since then, there has been a plethora of more recent publications focusing not only on the treatment outcomes but also on the toxicities associated with the treatment modality. Thus, because of the lack of contemporary internally validated studies and the availability of new literature, we undertook a systematic review and meta-analysis to review the literature as per the proposed methodologies.

METHODS

Search strategy: Studies will be reviewed from the 4 main databases including 1) PubMed 2) Web of Science 3) EMBASE 4) Scopus. We aim to collect the quantitative clinical studies and exclude the critical reviews and the systematic review and meta-analyses of the past. A time filter for the year 1st January 1990 to the current date of extraction that is, 1st November 2022 will be imposed. We will utilize the peer review of electronic search strategies (PRESS) 2015 guidelines to help provide a robust and comprehensive electronic literature search. PROSPERO was thoroughly accessed to review any ongoing or completed systematic reviews or meta-analyses based on our research question.

Participant or population: Adult patients (≥18 years) diagnosed with early or locally advanced renal cell carcinoma deemed medically inoperable will be assessed in the review. We will exclude studies

involving exclusively metastatic renal cell carcinoma.

Intervention: SBRT to renal mass.

Comparator: SBRT treatment with or without adjuvant treatment.

Study designs to be included: Relevant studies, including case reports, case series, case-control studies, and randomized control trials, will be included in this study.

Eligibility criteria: Adult patients (≥18 years) diagnosed with early or locally advanced renal cell carcinoma deemed medically inoperable will be assessed in the review.

Information sources: Studies will be reviewed from the 4 main databases including 1) PubMed 2) Web of Science 3) EMBASE 4) Scopus. We aim to collect the quantitative clinical studies and exclude the critical reviews and the systematic review and meta-analyses of the past. A time filter for the year 1st January 1990 to the current date of extraction that is, 1st November 2022 will be imposed. We will utilize the peer review of electronic search strategies (PRESS) 2015 guidelines to help provide a robust and comprehensive electronic literature search. After the literature search is completed, the results will be uploaded to Covidence (covidence.org) which is a web-based software platform that helps streamline the systematic reviews. Studies will be selected for inclusion following a three-stage process with help of Covidence.

1. Duplicates from the mentioned databases will be filtered out.
2. Two independent reviewers (VP and SZ) will screen the title and abstract of all the studies. Studies not meeting the eligibility criteria will be excluded. Conflict or discrepancy will be resolved through mutual discussion.
3. The full-text manuscripts of all screened studies from the second stage will be retrieved and final inclusion or exclusion decisions will be made by examining the full-text manuscripts. Two reviewers (VP and SZ) will then independently select studies that meet the predefined criteria. All disagreements will be discussed and resolved by an expert review author (AO). The reason for exclusion will be recorded. A flow chart of included and excluded studies at various stages of selection will be made following the PRISMA 2009 flow diagram (supplementary file 2).

Main outcome(s): The primary outcome will be recurrence-free survival (RFS), local control (LC), failure patterns after treatment, and high-risk factors for recurrence. Patient parameters (such as age), treatment parameters (such as SBRT dose, CTV and PTV margins, nephron-saving contouring, and adjuvant treatment), and disease parameters (such as size, histology, and grade) which may influence treatment will be assessed in the review. We have multiple parameters to inspect and identify its role in the failure of treatment failure. Failure refers to disease recurrence and can occur locally, regionally, or distantly. The identification of these variables will help future treatment strategies and may help reduce recurrences. The secondary outcome will be to calculate the mean age, mean tumor size, most common histology, most common grade, and survival outcomes such as disease-specific survival (DSS) and overall survival (OS) along with assessing the associated toxicities with SBRT treatment.

Quality assessment / Risk of bias analysis:
QUALITY APPRAISAL
The studies selected under the current review be evaluated using quality appraisal tools for quantitative studies produced by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (supplementary file 4). A copy of the completed checklists will be published with the review results as an additional file. For case reports and case series, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports (supplementary files 5 and 6) will be used to assess the risk of bias.
META-BIAS
We will evaluate for outcome reporting bias and compare the fixed effect estimate

against the random effects model to assess the possible presence of small sample bias in the published literature (i.e., in which the intervention effect is more beneficial in smaller studies). In the presence of a small sample bias, the random effects estimate of the intervention is more beneficial than the fixed effect estimate. The potential for reporting bias will be further explored using funnel plots if more than 10 studies are available.

Strategy of data synthesis / Subgroup analysis / Sensitivity analysis: Data from all the studies to be included will be extracted by two independent reviewers (VP and SZ) using Covidence. A list of biases will be generated, which will be critically evaluated by separate investigators. Discrepancies will be resolved through mutual discussions. Methodological heterogeneity will be evaluated separately by investigators by critically examining the study design. Statistical heterogeneity will be reported using the I2 and $\chi 2$ values. A value of $I2 > 60\%$ and $\chi 2$ with $p < 0.05$, was used to assess heterogeneity. The level of interventions and outcome measures will be tabulated to assess the applicability of the meta-analysis. Categorical variables, such as type of surgery and tumors in each study, will be presented using frequency and percentages. The continuous outcome variables such as resection margins and age will be reported as mean and standard deviation (SD or median with interquartile range (IQR) for continuous variables, depending on the reporting by different studies. The odds ratios (OR) comparing surgical excision without neo/and or adjuvant therapy against surgical excision with neo/and adjuvant therapy will be reported using a 95% confidence interval (CI) and p-value < 0.05. Local recurrence and regional and distant metastasis will be plotted using survival curves and hazard ratios (HR) with 95% CI will be calculated for the same. Forest plots for the primary and secondary outcomes will be reported. Further, other clinical variables of interest with adequate data will be reported. We are interested in determining the treatment outcomes with medically inoperable non-metastatic RCCs. The following parameters would be utilized to help refine the reviews and the results

1. Summarizing characteristics of the study
2. Identification of similar vs dissimilar studies
3. Synthesis as per data availability in each study
4. Rules for change in comparator if needed
5. Synthesis of characteristics of studies.

Language restriction: None.

Country(ies) involved: Canada.

Keywords: SBRT; inoperable Renal cell carcinoma; patterns of failure.

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