



Tactics for managing oligometastatic disease



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Navigating oligometastatic breast cancer: the role of stereotactic radiotherapy

In this interview, Imogen Locke (The Royal Marsden NHS Foundation Trust, UK) discusses the evolving role of stereotactic ablative radiotherapy (SABR) in oligometastatic and oligoprogressive breast cancer.

Locke explains the distinction between these two clinical scenarios, how timing and patient selection influence treatment decisions, and emerging evidence around metastasis-directed radiotherapy for ER-positive, HER2-negative patients on CDK4/6 inhibitors. Additionally, Locke walks us through a patient case study and highlights key radiotherapy trials seeking to answer the most pressing questions in breast cancer radiotherapy.

Can you give a brief overview of your talk at the Royal Marsden Breast Cancer Meeting?

I've been asked to give a talk on updates and clinical dilemmas in adjuvant radiotherapy. There's almost so much to talk about in that space that I thought I would talk about something different that's very live for me as a clinical issue at the moment, which is the management of oligometastatic breast cancer. This is breast cancer that's spread or has progressed in a very limited way. We're seeing new drugs coming through like CDK4/6 inhibitors, which are less toxic and more effective. Patients are living longer and they're living long enough to start to develop resistant breast cancer clones and develop metastases in a very limited way.

And the questions are, if we use metastasis-directed therapy, so that could be surgery or it could be ablation but in my world, that's SABR. The question is, by ablating those resistant oligometastases, do we prolong patients' survival? Do we give them longer on the same less toxic drug therapy? This is an unanswered question.



My talk will review what we know so far from prospective trials on oligometastatic disease and also a variant of that, which is oligoprogressive disease. I'm going to present the evidence that we have so far and ask the question: what is SABR adding? How should we select patients? I'm going to finish up by presenting a couple of patients who've come through my clinic doors in the last couple of months.

How do you approach the timing and sequencing of radiotherapy for oligometastatic patients?

It varies between oligometastatic disease and oligoprogressive disease. Oligometastatic disease is usually defined as being five or less metastases. They can appear at the time of primary diagnosis, and we call that synchronous oligometastatic disease.

Then there is metastases that develop sometime after the primary diagnosis, and we call that metachronous oligometastatic disease. At the moment in England, it's only the latter scenario where SABR, is actually commissioned because it's felt if there's a prolonged disease-free interval before the development of metastases, then it's more likely that ablation will have a role.

We generally like to see a patient established on systemic therapy for a number of months to be absolutely sure that they're in a true oligometastatic state before we would bring in stereotactic radiotherapy.

It's even more nuanced when looking at oligoprogressive disease, which is where there is more widespread metastatic disease. These patients have commenced on systemic therapy, which controls their disease for a period of time. Then you see the emergence of some resistant clones, so progression in a limited number of sites. Again, we would usually consider that to be four or five or less metastases. In this situation, it's much more difficult to know when to time ablative radiotherapy treatment.



Also, there's much less certainty about what we're achieving. In trials, so far, it hasn't been demonstrated that ablative therapy prolongs overall survival or even that it gives a progression-free survival advantage. Though there is starting to be a signal that perhaps in selected patients, those with ER-positive HER2-negative disease who are well controlled on a CDK4/6 inhibitor, may have some benefit from ablative radiotherapy in terms of treating disease that's progressing, which can allow them to stay on that low-toxicity systemic treatment for longer.

So, the paradigm is different. In oligometastatic disease, we're usually looking to ablate the disease in the hope of achieving a progression-free or overall survival advantage for the patient. Whereas in the oligoprogressive setting, the paradigm is much more about obtaining more value out of the systemic treatment that they're on, which is largely working well with low toxicity. And we hope to stop having to switch their systemic therapy to something that's more toxic.

Is toxicity a challenge you face when delivering radiotherapy to this patient group?

With stereotactic radiotherapy, the metastasis that you're ablating can be anywhere in the body. It can be in a bone, it could be in the lung, for example, and the toxicities will be different. But what is fundamental about stereotactic radiotherapy is that it's a very focused treatment.

So, whilst the metastasis gets a very high dose of radiotherapy, that dose of radiation falls off very quickly. So, in general, this is an extremely well-tolerated treatment and toxicity is not usually an issue at all.

Could you talk us through a SBRT case study?

The case that I'm going to present today is of a woman who presented with node-positive TNBC and had a very turbulent time with her chemotherapy.



She had an enormous amount of toxicity and so the treatment had to be stopped early. She then had adjuvant radiotherapy and a period where she was on no systemic therapy. Within a few months, she developed oligometastatic disease. I was asked to see her in clinic because she had one lesion in her lung that was progressing. I looked at the natural history of her disease. I'm always quite cautious in TNBC.

I think what you have to remember with stereotactic radiotherapy is what's your treatment goal? What are you trying to achieve for the patient? The other challenge is that sometimes radiology underestimates the burden of disease. For example, on a CT scan or a PET scan, you might see one solitary nodule or hotspot. But we know that there may be more widespread microscopic disease that we can't see.

In these situations, I sometimes do an interval image to get a feel for what's happening. In this woman's case, I did a PET scan 2 months after the one that she'd had before and sadly, she'd developed widespread liver disease.

In hindsight, if I treated that one nodule that was hot on the PET scan, it would have done her absolutely no good because she actually didn't have true oligoprogressive disease. So, I think the challenge for us is defining that oligoprogressive state better. That's probably going to be through more sophisticated imaging modalities, looking at the disease trajectory and perhaps things like circulating DNA will have a role, where we'll be able to better select patients for ablative therapies by looking at whose ctDNA mutation burden falls with systemic therapy.

Are there currently ctDNA tests for determining oligometastatic or oligoprogressive disease?

No, we don't use them routinely in the clinic. ctDNA mutation burden was measured as part of the [CURB trial](#), which was a trial in oligometastatic disease, looking at



ablative radiotherapy in a population of both breast cancer patients and lung cancer patients. This trial showed that for lung patients who saw a progression-free survival benefit from radiotherapy, this was matched by a fall in ctDNA burden, whereas in the breast group where we didn't see that benefit in the primary endpoint, the ctDNA didn't change. So, it may well emerge to be a useful part of the picture in defining true oligoprogression, but it's not live in the clinical setting at the moment.

What do you see as the most pressing research questions or unmet clinical needs in breast cancer radiotherapy?

I think we're lucky in the UK to have an absolutely fantastic portfolio of trials going on. The question that is really live at the moment in breast radiotherapy is: can every single patient having adjuvant breast radiotherapy be treated in just 1 week? We know that 70% of women who have breast radiotherapy after surgery at the moment are treated in 5 fractions over one week. But there are still some groups, for example, those having radiotherapy to their internal mammary lymph nodes, or those patients who are having a tumor bed boost, who currently are treated in 3 weeks.

From a practical point of view, the FAST-forward trial, which is ongoing, will answer that question. And I can see a very promising future where all breast radiotherapy for all patients in the adjuvant setting is done in 1 week.

Also, the limits of hypofractionation is a really interesting question. We have recruited fully to the PARABLE trial, which is the trial of protons for the adjuvant breast radiotherapy. It will be really interesting to see what niche role, if any, protons have for breast radiotherapy.

We have a whole array of trials looking at auxiliary treatment and the potential de-escalation of how much we treat the axilla.



As part of FAST-forward, we will answer the question surgeons keep asking us, which is whether five fractions of treatment is bad for oncoplastic surgery. We'd like to be able to give them the evidence to say, no, it's fine.

For radiotherapy sequencing, we've got the [PRADA2 trial](#) opening, which is looking at giving radiotherapy before DIEP reconstruction and looking at cosmetic outcomes.

So that's another question. There are a lot of unanswered questions, but we're lucky to have a lot of trials led in the UK that are going to answer them.

It sounds really exciting; we're on the cusp of answering those questions.

Breast radiotherapy, has changed so much in the time that I've been a consultant. When I started as a consultant, it was routine that all patients had 5 to 6 weeks of radiotherapy.

Now, for the vast majority of patients, they're having 1 week of radiotherapy and it has much less impact on their life and less toxicity. Now, I think the real unanswered question, and the one where we do need trials around, is how we personalize radiotherapy more to the biology of the disease.

That will be the next thing. We've got a lot of translational studies going on. So, each of those trials that I just talked about has a translational question attached to it as well.

Being able to personalize the radiotherapy to the underlying biology of the cancer and of the person will be the next focus. I think all the trials coming through in the future will need to be incorporating that kind of translational question. And also, as you mentioned earlier, incorporating ctDNA routinely into trials, will be the next big thing to do.



Interviewee profile:



Dr Imogen Locke has both a private and an NHS practice at The Royal Marsden. The service offers a comprehensive range of cutting-edge radiotherapy treatments including Intensity Modulated Radiotherapy (IMRT), Image Guided Radiotherapy (IGR), stereotactic radiotherapy and brachytherapy. She specializes in the treatment of breast and lung cancer.

She qualified at St Bartholomew's Hospital, London (UK) in 1994 and her subsequent oncological training was in London. She undertook research at The Institute of Cancer Research (London, UK) between 2003 and 2006, and was awarded an MD in 2008. Her research focused on the role of ductal lavage in the molecular risk assessment of women carrying germline mutations in the *BRCA1* and *BRCA2* genes who are at increased risk for developing breast cancer. Her current interests include the development of heart-sparing radiotherapy techniques for the treatment of breast cancer, stereotactic radiotherapy for the treatment of early-stage lung cancer and quality improvement activity.

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RAPID COMMUNICATION



'Perspectives of pulmonologists and thoracic surgeons on Oligometastatic disease: curability, treatment approaches, and disease trajectory'

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ABSTRACT

Background: Oligometastatic disease (OMD) is defined by a limited number of metastases, affecting treatment strategies and prognosis. This study evaluates the perspectives of pulmonologists and thoracic surgeons on the curability, treatment approaches, and disease trajectory of synchronous OMD, oligorecurrence, and oligoprogression.

Methods: A survey was conducted among pulmonologists, thoracic surgeons, and trainees at Yedikule Chest Disease and Thoracic Surgery Research and Training Hospital. Participants provided views on OMD's curability, treatment preferences, and confidence in discussing prognosis using Likert scales. Data were analyzed using descriptive statistics and comparative methods.

Results: Of 160 contacted participants, 60 (37.5%) completed the survey. Most respondents (86.6%) regarded synchronous OMD as curable, with 65% for oligorecurrence and only 23.4% for oligoprogression. Confidence in understanding synchronous OMD's trajectory significantly differed, with attending physicians at 67.9% versus trainees at 43.8% ($p < 0.05$). Thoracic surgeons had higher confidence in oligorecurrence (88.3%) than pulmonologists (46%, $p < 0.05$). A preference for combined systemic and local therapies was noted: 73.3% for synchronous OMD, 75% for oligorecurrence, and 78.4% for oligoprogression.

Conclusion: The study reveals diverse perspectives on OMD, highlighting the need for multidisciplinary collaboration and ongoing education to improve understanding and management of the disease.

PLAIN LANGUAGE SUMMARY

Doctors sometimes find cancer that has spread to a few other places in the body – this is called “oligometastatic disease.” In lung cancer, some experts believe this condition may still be curable, especially if treatment is started early. However, doctors do not always agree on what “curable” means in these situations. In our study, we asked 60 lung specialists – including pulmonologists and thoracic surgeons – how they view and treat different types of oligometastatic lung cancer. We gave them three case examples and asked about their opinions on whether these cases could be cured and how they would treat them. Most doctors believed that patients whose cancer spread at the same time it was diagnosed (“synchronous”) had a better chance of being cured. Fewer doctors thought that cancer returning later or growing again during treatment (“oligorecurrent” or “oligoprogressive”) was curable. This study shows that doctors' views differ, and it highlights the need for different specialties to work together when planning treatment for patients with oligometastatic lung cancer.

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1. Introduction

Oligometastatic disease (OMD) is characterized by a limited number of metastases, often confined to a single or a few organs, indicating a more restricted metastatic potential compared to widespread cancer [1]. Although there is no universal consensus, OMD typically involves up to five metastatic lesions [2]. Recent classifications offer a more detailed understanding of OMD's subtypes. Synchronous OMD refers to metastases identified at the same time as the primary cancer diagnosis, while oligorecurrence describes limited metastatic recurrence following an initial non-metastatic cancer diagnosis. Oligoprogression, on the other hand, involves the progression of a few metastatic lesions, while the

remaining disease stays stable [2]. These distinctions are critical for clinicians, as they directly impact management strategies.

Local ablative therapies (LATs), such as metastasectomy and stereotactic ablative radiotherapy (SABR), have shown promise in treating OMD. Metastasectomy is often considered in cases with resectable metastases and may improve survival in carefully selected patients [3], while SABR offers a precise, noninvasive option, especially for those unsuitable for surgery. LATs have been shown to significantly improve overall and progression-free survival (PFS) in patients with oligometastatic non-small cell lung cancer (NSCLC), particularly in synchronous or oligopersistent cases [4]. Recent studies suggest that in stage IV NSCLC with

Article highlights

- This study explores the perspectives of pulmonologists and thoracic surgeons on the curability and management of oligometastatic disease (OMD).
- A total of 60 specialists (43 pulmonologists, 17 thoracic surgeons) completed the survey, with a response rate of 37.5%.
- Synchronous OMD was considered curable by 86.6% of respondents, while only 23.4% considered oligoprogressive disease curable.
- Respondents expressed greater confidence and comfort in discussing prognosis for synchronous OMD than for oligorecurrence or oligoprogression.
- Perceived understanding of disease trajectory significantly influenced curability beliefs, especially for oligorecurrent disease ($p = 0.04$).
- Combined systemic and local therapies were the most commonly recommended treatment approach across all OMD subtypes.
- Significant differences were observed between pulmonologists and thoracic surgeons in understanding oligorecurrence ($p = 0.03$).
- The findings highlight the importance of multidisciplinary collaboration in OMD management and the need for educational efforts to address knowledge gaps.

oligometastases, LATs, including SABR, administered before maintenance chemotherapy, significantly enhance PFS, with a threefold improvement compared to maintenance chemotherapy alone [5]. Additionally, multicenter randomized trials have confirmed that LATs notably improve both PFS and overall survival in stage IV NSCLC patients with three or fewer metastases who have not progressed following initial systemic therapy [6,7]. These findings highlight the potential of aggressive local therapies to improve outcomes in OMD.

Several studies have explored the perspectives of medical and radiation oncologists on OMD [8–11]. While there is general agreement on treatment approaches, certain clinical scenarios still lack consensus, underscoring the need for stronger evidence [10]. Moreover, it is emphasized that treatment decisions for oligometastatic NSCLC should involve a multidisciplinary oncology board, including medical oncologists, pulmonologists, thoracic surgeons, and radiation oncologists [12].

Pulmonologists and thoracic surgeons are often involved in diagnosing and managing OMD. As evidence supporting the benefits of local therapies in OMD grows, the importance of multidisciplinary collaboration has become increasingly clear. A previous study assessed the perspectives of pulmonologists and oncologists on OMD, but the sample size was limited, comprising only 7 pulmonologists and 4 thoracic surgeons [13]. Since patients often consult pulmonologists first before being referred to thoracic surgeons for potential surgery or oncologists for cancer treatment, it is crucial for these specialists to be knowledgeable about OMD. This study aims to fill a gap in the literature by examining the perspectives of attending pulmonologists, thoracic surgeons, and trainees on OMD, emphasizing the need for integrated, collaborative approaches in patient care.

2. Methods

2.1. Study design

This study was designed as a survey research to evaluate the perspectives of pulmonologists and thoracic surgeons on OMD. The survey was adapted from a previous surveys on

oligometastatic cancer [8,14,15] which organized into three sections, each focusing on a different aspect of OMD: synchronous OMD, oligorecurrence, and oligoprogression. For each category, participants expressed their opinions on the curability of the disease using Likert scales. In addition, hypothetical patient scenarios specific to each OMD subtype were presented. These scenarios were adapted to reflect the different forms of OMD. In each case, participants were asked to propose treatment options and assess the relevance of various factors influencing their recommendations, using Likert scales. They were also asked to estimate the likelihood of achieving a cure in each scenario. Participants could skip questions on cases they felt unqualified to answer. At the end of the survey, respondents self-reported demographic details such as age, gender, medical specialty, level of training, and years of professional experience. The full version of the questionnaire used in this study, including all three sections and hypothetical patient scenarios, is available in the Supplementary Material.

2.2. Participants

The study included pulmonologists, thoracic surgeons, and trainees affiliated with Yedikule Chest Disease and Thoracic Surgery Research and Training Hospital, where approximately 700 lung cancer surgeries are performed annually. To ensure broad participation, no exclusion criteria were applied, allowing all pulmonologists and thoracic surgeons at the institution to take part. Invitations were sent via institutional e-mail on two occasions over a two-month period (March to May 2024).

2.3. Hypothetical patient scenarios provided in survey

Hypothetical patient scenarios were developed in accordance with the classification proposed by Guckenberger et al [16].

2.3.1. Case 1

A 60-year-old nonsmoking woman presented to the Chest Diseases Clinic with a persistent cough. Diagnostic tests revealed a 2 cm nodule in the left upper lobe of the lung, and a biopsy confirmed adenocarcinoma. Further imaging identified a single 1 cm metastatic lesion in the liver, leading to a diagnosis of oligometastatic lung cancer.

This case represents de-novo synchronous oligometastatic NSCLC, where the primary tumor and a single distant metastasis are detected at initial diagnosis. According to Guckenberger et al., this falls under de-novo oligometastatic disease, synchronous subtype.

2.3.2. Case 2

A 65-year-old woman, previously treated with surgery for lung cancer, presented with mild fatigue and weight loss ten months postoperatively. Imaging revealed metastatic disease in the lung (2 cm) and two regions of the liver (2 cm and 2.5 cm). A liver biopsy confirmed metastasis from lung cancer. The patient expressed a desire to maximize survival without sacrificing quality of life. In this case, aggressive treatment options aimed at extending survival while maintaining quality of life could be considered, with decisions based on the patient's overall health, extent of disease, and available therapies.

This case represents metachronous oligorecurrence, as the patient developed limited metastases more than six months after definitive local treatment and in the absence of ongoing systemic therapy. According to the multidimensional classification framework proposed by Guckenberger et al. [16], oligorecurrence refers to the reappearance of limited metastatic disease following a period of disease control achieved with local therapies. Therefore, this case aligns with both the time-based definition of metachronous OMD and the therapeutic-context-based definition of oligorecurrence.

2.3.3. Case 3

A 50-year-old man with a limited smoking history was incidentally found to have a 2 cm mass in the right upper lobe of the lung on a chest computer tomography (CT) scan. Biopsy confirmed lung adenocarcinoma without targetable mutations (e.g., EGFR, ALK). Staging scans revealed a 2 cm metastatic lesion on the contralateral pleura, multiple liver metastases (1–1.5 cm), and two subcentimeter brain metastases, all asymptomatic. Genetic profiling showed PD-L1 expression at 10%. The patient was treated with a combination of chemotherapy and immunotherapy. Follow-up Positron Emission Tomography (PET)/CT scans showed a significant reduction in most disease sites, except for two liver metastases, which had slowly increased in size from 1–1.5 cm to 1.6–1.8 cm with heightened avidity. The patient, with an Eastern Cooperative Oncology Group (ECOG) performance status of 1, was referred for a multidisciplinary evaluation, expressing a preference for extending survival as much as possible, even if it impacted quality of life.

This case corresponds to oligoprogressive disease, where systemic therapy has controlled most disease sites, but a few metastatic lesions continue to progress. According to Guckenberger et al., this aligns with induced oligoprogression, as progression is observed under active systemic therapy.

2.4. Data analysis

Data analysis was conducted using Jamovi software version 2.5.3.0. Descriptive statistics were presented as mean $\pm$ standard deviation, median (minimum-maximum), or *n* (%), depending on the variable type. Responses were included in the analysis based on the extent of survey completion. Partial responses, where participants answered only some general or case-specific questions related to any OMD subtype, were also incorporated into the analysis.

The raw data were prepared and coded for quantitative analysis. Confidence in treatment decisions, understanding of prognosis, and perceptions of OMD curability were treated as categorical variables. Categorical data were compared using the χ^2 test or Fisher's exact test as appropriate. Likert scale responses for factors influencing treatment decisions were converted into numerical scores (1 = strongly disagree, 2 = somewhat disagree, 3 = neutral, 4 = somewhat agree, 5 = strongly agree), with mean scores calculated and presented in tables. A *p*-value of <0.05 was considered statistically significant.

3. Results

Out of 160 contacted participants, 60 completed the survey, yielding a 37.5% response rate. Of these, 43 (71.7%) were pulmonologists (48.8% attending physicians, 51.2% trainees), and 17 (28.3%) were thoracic surgeons (41.2% attending physicians, 58.8% trainees). The median professional experience was 7 years (1–44), and the median age was 31 years (25–66). Of the respondents, 23 (38.3%) were male. A detailed summary of participant characteristics is presented in Table 1.

3.1. Perceptions on synchronous OMD

Most respondents (86.6%) believed synchronous OMD is curable. A small minority (6.7%) disagreed. Regarding the frequency of using terms like “cure” or “curable,” 71.7% reported using these “sometimes,” or “rarely,” 25% “frequently,” or “always,” while 3.3% never used these terms. In terms of understanding the disease trajectory, 55% felt confident, while 26.6% disagreed, and 18.3% were neutral. There was no statistically significant association between participants' self-reported understanding of synchronous OMD and their belief in its curability ($p = 0.16$). Among those who strongly or somewhat agreed that they understood the disease trajectory, 51.7% believed synchronous OMD was curable, while 20.7% somewhat disagreed and 6.9% strongly disagreed. In contrast, among those who somewhat or strongly disagreed with understanding the disease trajectory, 66.7% did not consider it curable. Although a trend was observed, the difference was not statistically significant.

Regarding comfort in discussing prognosis, 51.7% felt comfortable, with 33.3% feeling uncomfortable and 15% remaining neutral. When evaluating treatment recommendations for hypothetical cases of synchronous OMD, 73.3% favored a combination of systemic and local therapies, 5% chose systemic therapy alone, and 3.3% preferred local therapy only. Confidence in treatment recommendations varied, with 71.6% somewhat or strongly agreeing. No significant differences in treatment recommendations were observed based on views of curability. The key factors influencing treatment decisions are summarized in Table 2.

When asked whether they believed this patient's cancer is curable, 86.7% of respondents strongly or somewhat agreed, 5% somewhat disagreed, and 8.3% were neutral.

3.2. Perceptions on Oligorecurrent disease

Regarding curability, 65% believed oligorecurrent disease is curable. Meanwhile, 23.4% disagreed. When discussing prognosis, 80% reported using terms like “cure” “sometimes,” or

Table 1. Baseline characteristics.

Parameters	Value (<i>n</i> = 60)
Age (year), median (range)	31 (25–66)
Male sex, <i>n</i> (%)	23 (38.3)
Specialty, <i>n</i> (%)	
Pulmonologist	43 (71.7)
Thoracic surgeon	17 (28.3)
Level of training, <i>n</i> (%)	
Attending physician	32 (53.3)
Trainee	28 (46.7)
Years of working, median (range)	7 (1–44)

Table 2. Factors for treatment decision making in synchronous OMD.

Factors	Strongly disagree	Somewhat disagree	Neutral	Somewhat agree	Strongly agree	Rating (mean)*
Patient age	2 (3.3)	2 (3.3)	2 (3.3)	15 (25)	39 (65)	4.45
Comorbidities and performance status	2 (3.4)	1 (1.7)	1 (1.7)	10 (16.9)	45 (76.3)	4.61
Extent of primary tumor	1 (1.7)	0	2 (3.3)	14 (23.3)	43 (71.7)	4.63
Number of metastases	0	0	0	9 (15)	51 (85)	4.85
Osseous versus extraosseous location	2 (3.3)	1 (1.7)	2 (3.3)	12 (20)	43 (71.7)	4.55
Extracranial versus intracranial location	3 (5)	0	4 (6.7)	20 (33.3)	33 (55)	4.33
Nodal versus nonnodal involvement	1 (1.7)	2 (3.3)	2 (3.3)	7 (11.7)	48 (80)	4.65
Locoregional versus distant metastases	1 (1.7)	1 (1.7)	2 (3.4)	6 (10.2)	49 (83.1)	4.71
Primary cancer histology	1 (1.7)	3 (5)	4 (6.7)	16 (26.7)	36 (60)	4.38
Biomarkers of primary cancer ⁺	3 (5.1)	2 (3.4)	6 (10.2)	14 (23.7)	34 (57.6)	4.25
Patient symptoms/quality of life	3 (5.2)	2 (3.4)	1 (1.7)	20 (34.5)	32 (55.2)	4.31
Risk of toxicity from local treatment or systemic therapy	3 (5)	1 (1.7)	6 (10)	23 (38.3)	27 (45)	4.16
Cost	8 (13.6)	5 (8.5)	13 (22)	25 (42.4)	8 (13.6)	3.33
Risk of harm due to delay of systemic therapy	3 (5.1)	4 (6.8)	4 (6.8)	21 (35.6)	27 (45.8)	4.10
Benefit of increased time off systemic therapy	3 (5.1)	6 (10.2)	12 (20.3)	22 (37.3)	16 (27.1)	3.71
Patient preference	2 (3.4)	1 (1.7)	5 (8.5)	16 (27.1)	35 (59.3)	4.37

Abbreviation: OMD = oligometastatic disease. *Likert scale scoring: 1 = strongly disagree, 2 = somewhat disagree, 3 = neutral, 4 = somewhat agree, 5 = strongly agree. ⁺ "Biomarkers of primary cancer" refers to molecular and immunohistochemical markers such as EGFR, ALK, ROS1, and PD-L1, which influence treatment decisions in non-small cell lung cancer.

"rarely," 15% "frequently," or "always," and 5% "never." A good understanding of the disease trajectory was reported by 58.4%, while 18.4% disagreed, and 23.3% were neutral. There was a statistically significant association between participants' self-reported understanding of oligorecurrent disease and their belief in its curability ($p = 0.04$). Among those who strongly or somewhat agreed that they understood the disease trajectory, 57.6% considered oligorecurrent disease curable, while only 9.1% somewhat disagreed and 6.1% strongly disagreed. In contrast, among those who somewhat or strongly disagreed with understanding the disease trajectory, 40% did not consider it curable.

Comfort in discussing prognosis was noted by 43.3%, with 40% feeling uncomfortable and 16.7% neutral. For hypothetical oligorecurrence treatment scenarios, 75% preferred combining systemic and local therapies, 16.7% opted for systemic therapy alone, and 8.3% chose local therapy only. Confidence in treatment decisions varied: 60% somewhat or strongly agreed, 17% somewhat or strongly disagreed. Specifically, treatment preferences varied according to beliefs about oligorecurrence's curability ($p = 0.04$). Respondents who strongly disagreed with oligorecurrence being curable mostly preferred a combination of systemic and local therapies (75%), with 25% opting for systemic therapy alone; none chose local therapy alone. Those who somewhat disagreed were evenly split between systemic therapy alone and a combination of systemic and local therapies, with none selecting local therapy alone. Respondents who strongly agreed on curability preferred a combination of therapies (66.7%), with 16.7% choosing systemic alone and 16.7% choosing local alone. Among those who somewhat agreed, the majority preferred combined therapies (84.8%), with fewer opting for systemic (9.1%) or local therapy alone (6.1%). Those neutral about curability mostly favored combined therapies (71.4%), with 28.6% choosing local therapy alone and none selecting systemic therapy alone. Factors influencing treatment choices are summarized in Table 3.

When asked whether they believed this patient's cancer is curable, 50% of respondents strongly or somewhat agreed, 28.3% somewhat or strongly disagreed, and 21.7% were neutral.

3.3. Perceptions on Oligoprogressive disease

Only 23.4% considered oligoprogressive disease curable. A majority (65%) disagreed. In terms of using the term "cure," 66.6% reported using it "sometimes," or "rarely," 28.3% "never," 5% "frequently," or "always." Confidence in understanding disease trajectory was reported by 43.4%, with 26.7% disagreeing and 30% neutral. There was no statistically significant association between participants' self-reported understanding of oligoprogressive disease and their belief in its curability ($p = 0.06$), although a trend was observed. Among those who strongly or somewhat agreed that they understood the disease trajectory, 38.5% considered oligoprogressive disease curable, whereas 7.7% somewhat disagreed and 15.4% strongly disagreed. In contrast, among those who somewhat or strongly disagreed with understanding the disease trajectory, 33.3% did not consider it curable.

Comfort in discussing prognosis was noted by 38.3%, while 43.3% felt uncomfortable, and 18.3% were neutral. For treatment recommendations regarding oligoprogressive OMD, 78.4% preferred a combination of systemic and local therapies: 36.7% would treat all growing metastatic sites locally, 41.7% all metastatic sites, and 11.7% chose systemic therapy alone. 5 respondents preferred local therapy only (1.7% all sites, 3.3% growing sites). Confidence in recommendations varied, with 40% somewhat or strongly agreeing. No significant differences were found in treatment recommendations based on curability views. Factors influencing treatment decisions are summarized in Table 4.

Regarding curability beliefs for this patient, 1.7% strongly agreed, 45% somewhat agreed, 18.3% somewhat disagreed, 18.3% strongly disagreed, and 16.7% were neutral.

The most frequently considered factors in treatment decisions for all OMD subtypes were locoregional versus distant metastasis and the number of metastases. The least considered factors varied by subtype: for synchronous OMD and oligorecurrent disease, these were time off systemic therapy and cost; for oligoprogressive disease, it was the risk of treatment toxicity.

Table 3. Factors for treatment decision making in oligorecurrent disease.

Factors	Strongly disagree	Somewhat disagree	Neutral	Somewhat agree	Strongly agree	Rating (mean)*
Patient age	3 (5.2)	2 (3.4)	3 (5.2)	10 (17.2)	40 (69)	4.41
Comorbidities and performance status	3 (5.1)	2 (3.4)	1 (1.7)	9 (15.3)	44 (74.6)	4.50
Extent of primary tumor	5 (8.6)	2 (3.4)	3 (5.2)	15 (25.9)	33 (56.9)	4.18
Number of metastases	1 (1.7)	0	2 (3.4)	12 (20.3)	44 (74.6)	4.66
Osseous versus extraosseous location	4 (6.9)	1 (1.7)	2 (3.4)	10 (17.2)	41 (70.7)	4.43
Extracranial versus intracranial location	3 (5.2)	1 (1.7)	3 (5.2)	12 (20.7)	39 (67.2)	4.43
Nodal versus nonnodal involvement	2 (3.4)	2 (3.4)	3 (5.1)	12 (20.3)	40 (67.8)	4.45
Locoregional versus distant metastases	1 (1.7)	1 (1.7)	2 (3.4)	10 (16.9)	45 (76.3)	4.64
Primary cancer histology	3 (5.2)	3 (5.2)	5 (8.6)	12 (20.7)	35 (60.3)	4.25
Biomarkers of primary cancer ⁺	3 (5.2)	2 (3.4)	3 (5.2)	17 (29.3)	33 (56.9)	4.29
History of treatments of primary cancer	2 (3.4)	2 (3.4)	3 (5.1)	11 (18.6)	41 (69.5)	4.47
Time to progression	3 (5.1)	2 (3.4)	3 (5.1)	13 (22)	38 (64.4)	4.37
Patient symptoms/quality of life	2 (3.4)	2 (3.4)	1 (1.7)	12 (20.3)	42 (71.2)	4.52
Risk of toxicity from local treatment or systemic therapy	2 (3.4)	1 (1.7)	4 (6.8)	18 (30.5)	34 (57.6)	4.37
Cost	8 (13.8)	5 (8.6)	9 (15.5)	24 (41.4)	12 (20.7)	3.46
Risk of harm due to delay of systemic therapy	2 (3.4)	3 (5.1)	4 (6.8)	16 (27.1)	34 (57.6)	4.30

*Likert scale scoring: 1 = strongly disagree, 2 = somewhat disagree, 3 = neutral, 4 = somewhat agree, 5 = strongly agree. ⁺ "Biomarkers of primary cancer" refers to molecular and immunohistochemical markers such as EGFR, ALK, ROS1, and PD-L1, which influence treatment decisions in non-small cell lung cancer.

Table 4. Factors for treatment decision making in oligoprogressive disease.

Factors	Strongly disagree	Somewhat disagree	Neutral	Somewhat agree	Strongly agree	Rating (mean)*
Patient age	2 (3.3)	0	1 (1.7)	14 (23.3)	43 (71.7)	4.60
Comorbidities and performance status	1 (1.7)	1 (1.7)	1 (1.7)	10 (16.7)	47 (78.3)	4.68
Extent of primary tumor	1 (1.7)	2 (3.3)	2 (3.3)	17 (28.3)	38 (63.3)	4.48
Number of metastases	0	1 (1.7)	2 (3.4)	13 (22)	43 (72.9)	4.70
Osseous versus extraosseous location	1 (1.7)	2 (3.3)	2 (3.3)	12 (20)	43 (71.7)	4.56
Extracranial versus intracranial location	1 (1.7)	2 (3.3)	3 (5)	13 (21.7)	41 (68.3)	4.51
Nodal versus nonnodal involvement	2 (3.3)	1 (1.7)	3 (5)	10 (16.7)	44 (73.3)	4.55
Locoregional versus distant metastases	0	0	1 (1.7)	13 (21.7)	46 (76.7)	4.75
Primary cancer histology	1 (1.7)	0	3 (5)	13 (21.7)	43 (71.7)	4.61
Biomarkers of primary cancer ⁺	2 (3.4)	0	3 (5.2)	15 (25.9)	38 (65.5)	4.50
History of treatments of primary cancer	1 (1.7)	1 (1.7)	2 (3.4)	12 (20.3)	43 (72.9)	4.61
History of treatments for metastatic sites	2 (3.3)	0	3 (5)	16 (26.7)	39 (65.5)	4.50
Time to progression	2 (3.4)	0	2 (3.4)	11 (18.6)	44 (74.6)	4.61
Patient symptoms/quality of life	2 (3.4)	2 (3.4)	3 (5.1)	14 (23.7)	38 (64.4)	4.42
Risk of toxicity from local treatment or systemic therapy	7 (11.9)	4 (6.8)	9 (15.3)	22 (37.3)	17 (28.8)	3.64
Cost	1 (1.7)	2 (3.3)	5 (8.3)	17 (28.3)	35 (58.3)	4.38

*Likert scale scoring: 1 = strongly disagree, 2 = somewhat disagree, 3 = neutral, 4 = somewhat agree, 5 = strongly agree. ⁺ "Biomarkers of primary cancer" refers to molecular and immunohistochemical markers such as EGFR, ALK, ROS1, and PD-L1, which influence treatment decisions in non-small cell lung cancer.

3.4. Comparative analysis

The study compared 43 pulmonologists (71.7%) with 17 thoracic surgeons (28.3%). There were no significant differences in median age (31 vs. 32 years; $p = 0.3$) or years of experience (7 vs. 6 years; $p = 0.7$). However, a significant disparity was noted in sex distribution, with 25.6% of pulmonologists being male compared to 70.6% of thoracic surgeons ($p = 0.001$). Training levels were similar, with 48.8% of pulmonologists and 41.2% of thoracic surgeons serving as attending physicians. In a further analysis, 28 attending physicians (46.7%) were compared to 32 trainees (53.3%). Attending physicians were significantly older (median age 41.5 vs. 29 years; $p < 0.001$) and had more experience (16.5 vs. 4.25 years; $p < 0.001$). There was no significant difference in sex distribution, with 35.7% of attending physicians being male compared to 40.6% of trainees ($p = 0.6$).

Among the 60 respondents, 86.6% agreed that synchronous OMD is curable, while 6.7% disagreed. For oligorecurrence, 60% believed it was curable, with 23.4% disagreeing. A mere 23.4% considered oligoprogression to be curable, with 65% disagreeing (Table 5). There were no significant differences between

pulmonologists and thoracic surgeons or between attending physicians and trainees regarding opinions on curability ($p > 0.05$). Understanding of the disease trajectory was limited across subtypes: 55% for synchronous OMD, 58.4% for oligorecurrence, and 43.4% for oligoprogression. Comfort in discussing prognosis followed a similar pattern: 51.7% for synchronous OMD, 43.3% for oligorecurrence, and 38.3% for oligoprogression. Notably, a significant difference was found in understanding oligorecurrence, with 46% of pulmonologists and 88.3% of thoracic surgeons reporting a good understanding ($p = 0.03$). Additionally, attending physicians demonstrated a better understanding of synchronous OMD compared to trainees (67.9% vs. 43.8%; $p < 0.01$).

4. Discussion

In this study, we explored the perspectives of pulmonologists and thoracic surgeons on OMD, focusing on treatment strategies, curability, prognosis, and disease trajectory. Our results showed that 86.6% of respondents believed synchronous OMD to be curable,

Table 5. Pulmonologists' and thoracic surgeons' views on curability of oligometastatic disease.

Item	Strongly/somewhat disagree	Neutral	Strongly/somewhat agree
Synchronous oligometastatic disease (<i>n</i> = 60)			
Synchronous oligometastatic disease is curable.	4 (6.7)	4 (6.7)	52 (86.6)
I have a good understanding of the disease trajectory of a patient with synchronous oligometastatic disease.	16 (26.6)	11 (18.3)	33 (55)
I feel comfortable discussing prognosis with a patient with synchronous oligometastatic disease.	20 (33.3)	9 (15)	31 (51.7)
Oligorecurrent disease (<i>n</i> = 60)			
Oligorecurrent cancer is curable.	14 (23.4)	7 (11.7)	39 (65)
I have a good understanding of the disease trajectory of a patient with oligorecurrent cancer.	11 (18.4)	14 (23.3)	34 (58.4)
I feel comfortable discussing prognosis with a patient with oligorecurrent cancer.	24 (40)	10 (16.7)	26 (43.3)
Oligoprogressive disease (<i>n</i> = 60)			
Oligoprogressive cancer is curable.	39 (65)	7 (11.7)	14 (23.4)
I have a good understanding of the disease trajectory of a patient with oligoprogressive cancer.	16 (26.7)	18 (30)	26 (43.4)
I feel comfortable discussing prognosis with a patient with oligoprogressive cancer.	26 (43.3)	11 (18.3)	23 (38.3)

compared to 65% for oligorecurrence and 23.4% for oligoprogression. A notable difference was observed in the confidence levels regarding the understanding of synchronous OMD trajectory between attending physicians (67.9%) and trainees (43.8%). Interestingly, while pulmonologists and thoracic surgeons had similar views on synchronous and oligoprogressive OMD, a marked difference was seen for oligorecurrent disease, with 46% of pulmonologists versus 88.3% of thoracic surgeons confident in their understanding of its trajectory. These findings underscore the critical role of multidisciplinary collaboration in the management of OMD.

In patients with synchronous OMD NSCLC, multimodal treatments have shown promising outcomes [17]. A retrospective study involving 51 patients treated with surgery or radiotherapy reported a median survival of 42 months, with 2- and 5-year survival rates of 62% and 34.4%, respectively, supporting the value of aggressive local treatment in select cases. While synchronicity in oligometastatic lung cancer did not significantly affect overall survival compared to patients with locally advanced lung cancer, progression-free survival (PFS) was worse in the OMD group [18]. A survey assessing the views of medical and radiation oncologists on the curability of synchronous OMD found that 62.4% considered it curable [8]. Conducted two years ago, this study likely reflects a period with fewer advancements in treatment options. Given the rapid progression of OMD research, perceptions of curability may have evolved. In our study, which reflects current perspectives in light of recent developments, 82% of pulmonologists and thoracic surgeons shared this belief. According to joint ASTRO and ESTRO guidelines, in the absence of robust phase 3 trials, the integration of local therapies with systemic treatments is recommended for extracranial oligometastatic NSCLC, emphasizing a patient-centered, multidisciplinary approach [19]. In our findings, 73.3% of respondents favored a combination of systemic and local therapies for synchronous OMD, consistent with these guidelines, while 5% opted for systemic therapy alone and 3.3% preferred local therapy only. This highlights a strong preference for combined treatment strategies, in line with current clinical recommendations.

In our study, 65% of participants believed oligorecurrence to be curable, a higher rate than the 46.2% reported by Cho et al. [8]. This view is reinforced by recent studies on metachronous brain-only oligorecurrence in NSCLC,

where patients treated with definitive local therapy achieved long-term survival, with a median overall survival of 38.9 months and substantial 2- and 5-year survival rates. Moreover, the study found no significant benefit of adding systemic therapy over local treatment alone, emphasizing the potential for favorable outcomes with local therapy in oligorecurrent cases [20]. Regarding treatment preferences for oligorecurrent disease, 75% of respondents favored a combination of systemic and local therapies, while 16.7% opted for systemic therapy alone, and 8.3% chose local therapy only. Confidence in treatment recommendations varied, with significant differences observed based on curability beliefs ($p = 0.04$). Respondents who strongly disagreed with oligorecurrence's curability preferred a combination of systemic and local therapies (75%) or systemic therapy alone (25%). Those somewhat disagreeing were evenly split between systemic therapy alone and combined therapies. Conversely, those strongly agreeing with curability favored combined therapies (66.7%), while those somewhat agreeing mostly preferred combined therapies (84.8%). Neutral respondents also favored combined therapies (71.4%) or local therapy alone (28.6%). These findings suggest that curability perceptions significantly influence treatment choices, with less curability seen leading to more systemic therapy recommendations.

Although metachronous OMD is commonly associated with a more favorable prognosis than synchronous OMD [21], this view is not universally supported [22]. In our survey, only 50% of respondents considered the oligorecurrent/metachronous case curable, compared to 86.7% for the synchronous case. This may reflect real-world decision-making, where factors like tumor biology, metastatic site, and patient characteristics influence curability perceptions beyond time interval alone. Additionally, as all respondents were pulmonologists or thoracic surgeons, their perspectives may differ from those of medical oncologists. This highlights the importance of multidisciplinary collaboration in oligometastatic NSCLC management.

For oligoprogressive disease, 78.4% of respondents preferred a treatment regimen combining systemic and local therapies. Specifically, 36.7% favored local treatment for all sites of growing metastatic disease, 41.7% chose local therapy for all metastatic sites, and 11.7% opted for systemic treatment alone. A study on oligoprogressive small cell lung cancer (SCLC) found that while stereotactic body radiotherapy (SBRT)

achieved successful local control, most patients still experienced distant relapse, and overall survival remained limited [23]. These results suggest that although local treatment can be effective, the risk of distant relapse is significant, and long-term responses are infrequent. Our study indicated that 23.4% of participants considered oligoprogressive disease curable, compared to 13.5% in Cho et al.'s study [8], reflecting a more optimistic outlook among our cohort.

Responses in our study regarding the curability of all OMD subtypes were more optimistic and confident than those reported by Cho et al. [8] among oncologists. This shift may be attributed to recent advancements in understanding OMD's curability and increased prominence in national and international discussions. Additionally, our center's specialization in pulmonary diseases may have contributed to heightened awareness and familiarity with these specific conditions.

The role of molecular biomarkers, including EGFR [24] and ALK mutations [7], as well as PD-L1 expression [25], in treatment decision-making showed varying levels of agreement across different OMD subtypes. While most respondents acknowledged their importance, support was strongest in oligoprogressive disease (mean = 4.50), followed by oligorecurrent (mean = 4.29) and synchronous OMD (mean = 4.25). This trend suggests that biomarkers may play a more decisive role in later-stage OMD subtypes, potentially guiding systemic therapy choices. In contrast, treatment strategies for synchronous OMD might be influenced more by disease burden and anatomical distribution than molecular markers. These findings highlight the evolving role of biomarker-driven decision-making in oligometastatic NSCLC and underscore the need for further research on their impact in clinical practice.

Our analysis revealed that participants who reported a better understanding of OMD were more likely to consider oligorecurrent disease curable ($p = 0.04$), while no statistically significant association was found for synchronous ($p = 0.16$) or oligoprogressive disease ($p = 0.06$), though a trend was observed. These findings suggest that confidence in disease trajectory comprehension may influence curability perceptions, particularly in oligorecurrent disease. While this could reflect true expertise, potential cognitive biases cannot be ruled out, highlighting the need for further education and standardized guidelines in OMD management.

In the treatment of oligometastatic NSCLC, surgery has traditionally been a primary approach. Early systematic reviews indicated that over half of all patients underwent surgical intervention [26]. Key surgical strategies include aggressive upfront resection of the primary tumor, followed by resection or SBRT of metastatic lesions, and neoadjuvant systemic treatment with subsequent resection after restaging [27]. The objective of surgery is to remove the tumor burden, control micrometastatic disease, and potentially improve overall survival [28]. The critical role of surgery in managing OMD underscores the importance of thoracic surgeons' expertise. Our study found that 70.6% of thoracic surgeons reported a strong understanding of the disease trajectory in synchronous OMD, compared to 88.3% for oligorecurrence and 47.1% for oligoprogressive disease. In contrast, 48.9% of pulmonologists had a strong understanding of synchronous OMD, 46.5%

for oligorecurrence, and 41.8% for oligoprogressive disease. A significant difference in understanding the trajectory of oligorecurrence was noted between thoracic surgeons and pulmonologists ($p = 0.03$), suggesting that pulmonologists may require more in-depth knowledge, particularly regarding oligorecurrence. Overall, understanding of oligoprogressive disease was lower across both groups, highlighting a general need for enhanced expertise and information about this condition. The higher confidence among thoracic surgeons in understanding OMD at our hospital may be attributed to the high volume of lung cancer surgeries performed. With approximately 700 lung cancer surgeries annually, accounting for about 50% of all surgeries, thoracic surgeons gain extensive experience and expertise, likely enhancing their understanding of OMD. Conversely, pulmonologists, who deal with a broader range of pulmonary conditions beyond lung cancer, may have less specialized experience with OMD. Additionally, their reduced exposure to surgical interventions compared to thoracic surgeons may impact their familiarity with disease progression and treatment outcomes in OMD. This difference in clinical focus and experience likely contributes to the observed disparity in understanding between the two specialties.

Although not separately evaluated in our survey, oligopersistent disease may represent a scenario where noninvasive local therapies, such as SBRT, could be preferred over surgery, particularly in patients with persistent but stable lesions and maintained systemic control [16].

The differences between our findings and those of Cho et al. [8] may not be solely attributable to the time gap between 2023 and 2025. They may instead reflect differences in participant characteristics, institutional practices, or regional treatment strategies. Moreover, the preliminary results of the NRG-LU002 trial presented in 2024 [29], which did not demonstrate a clear progression-free survival benefit of local consolidative therapy in this setting, may have further contributed to the ongoing uncertainty regarding the role of local therapies in oligometastatic NSCLC. This evolving evidence base underscores the need for further prospective studies to refine treatment strategies for OMD.

Our results reveal that trainees perceive their understanding of the synchronous OMD trajectory as significantly lower compared to attending physicians. This highlights the need to enhance education on OMD for both thoracic surgery and pulmonology trainees. A deeper understanding of OMD is essential for effective clinical practice and improving patient outcomes. Thus, providing more comprehensive training and resources on this topic is crucial to bridge the knowledge gap and better prepare trainees for their future roles.

In our study, the factors most frequently considered were the distinction between locoregional and distant metastasis and the number of metastases. The least considered factors varied by OMD subtype: for synchronous OMD and oligorecurrent disease, these were the benefit of extended time off systemic therapy and cost; for oligoprogressive disease, the risk of treatment toxicity was least considered. In contrast, Cho et al. [8] identified the number of metastases, toxicity risk, and patient preference as the top factors across all subtypes, with cost and nodal involvement being least important. Our

findings emphasize the importance of metastatic location in treatment planning, a factor less highlighted by Cho et al. [8]. Additionally, the differing emphasis on patient preference and toxicity risk suggests variations in clinical decision-making practices.

5. Limitations

This study is a single-center cross-sectional analysis conducted at a hospital specializing exclusively in pulmonary diseases. As such, the findings may not be generalizable to other health-care settings with different patient populations or treatment approaches. Another limitation of our study is that oligopersistent disease was not included as a separate category in our survey. Our study focused on synchronous, oligorecurrent, and oligoprogressive disease based on established classifications. However, oligopersistent disease represents a distinct clinical entity where persistent but stable metastatic lesions remain after systemic therapy, and its management may differ from other OMD subtypes. Future studies should specifically assess treatment approaches for oligopersistent disease.

6. Conclusion

This study reveals varied perspectives on OMD among pulmonologists and thoracic surgeons. A majority of respondents consider synchronous OMD to be curable (86.6%), whereas fewer view oligorecurrence (65%) and oligoprogression (23.4%) as curable. Thoracic surgeons exhibit greater confidence in understanding OMD, particularly regarding oligorecurrence, compared to pulmonologists. Since pulmonologists, including specialists and trainees, are often the initial point of contact for diagnosing OMD before referring patients for surgical intervention, there is a pressing need to enhance their understanding of these conditions. The preference for combined systemic and local therapies is consistent with current guidelines; however, the variations in opinions regarding treatment efficacy, especially for oligoprogressive disease, underscore the necessity for improved education and greater multidisciplinary collaboration.

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ChatGPT (OpenAI, GPT-4, March 2024 version) was used to improve the language and clarity of the manuscript. The final content was written and reviewed by the authors.

Author contributions

Celal Satıcı contributed to the conception and design of the study, supervised the project, participated in manuscript writing, and performed the statistical analyses. **Aysegül Erinc** was involved in manuscript writing and critical revision. **Inanc Yazici** contributed to data collection and manuscript writing. **Damla Azakli** was involved in data collection, manuscript writing, and performed the statistical analyses. All authors reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

Disclosure statement

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Ethical declaration

Our study was conducted in accordance with the Declaration of Helsinki. The local institutional ethics committee approved the study protocol (Ethics approval number: 2023–470). All participants provided informed consent prior to survey initiation. In this online study, informed consent was obtained by presenting detailed information about the study's purpose, content, and voluntary nature on the first page of the questionnaire. Participants indicated their consent by voluntarily proceeding to complete the survey.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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 - **An ongoing large-scale trial relevant to the therapeutic strategies discussed by our respondents.**

REVIEW



Economic evaluation of stereotactic radiotherapy and stereotactic radiosurgery technologies in the treatment of cancers: a systematic review

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ABSTRACT

Introduction: This systematic review study investigated the cost-effectiveness of stereotactic radiotherapy (SRT) and stereotactic radiosurgery (SRS) for treatment of various types of cancers.

Methods: PubMed, Scopus, and Web of Science were searched from 30 December 1990 to 1 January 2023. The entered studies were screened in accordance with the inclusion criteria. The inclusion criteria encompassed all types of economic evaluation studies that investigated SRT/SRS technologies in the treatment of various cancers.

Results: A total of 47 articles were included in the review. The findings suggest that the use of Linear accelerator technology for the treatment of lung cancer (8 out of 12 studies) and prostate cancer (4 out of 5 studies) was a cost-effective strategy. Linear accelerator was found to be cost-effective in the treatment of liver metastases and liver cancer (2 out of 5 studies). All of the included studies that used Gamma Knife technology in brain metastases reported Gamma-Knife was a cost-effective treatment. Furthermore, in the treatment of prostate and liver cancer, proton therapy was identified as a cost-effective option than other treatments.

Conclusions: This study confirms that SRT/SRS is a cost-effective procedure for the treatment of various types of cancers. Therefore, it is recommended to use SRT/SRS technology for optimal use of resources.

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Cost-effectiveness; stereotactic radiosurgery; linear accelerator; Gamma Knife; proton therapy; cancer

1. Introduction

During recent decades, the global population has witnessed an epidemiological transition in which the share of non-communicable diseases has increased in the total disease burden. In this epidemiological transition, accompanied by an increase in the elderly population, health sector expenditures have significantly increased due to the introduction of advanced technologies to deal with these diseases [1,2]. This situation has caused health economics related to non-communicable diseases, such as cancer, to become significantly more prominent, and economic evaluation studies have been implemented for the optimal use of treatment resources and the reduction of health sector expenditures. Economic evaluation assesses the costs and consequences of health intervention(s) [3]. Life years gained (LYG) and health-related quality of life (HRQoL) are two important outcomes in economic evaluation. These outcomes have been widely used to evaluate therapeutic interventions and describe the severity of disease [4,5]. In recent decades, an intervention that has been able to significantly improve HRQoL and LYG is

stereotactic radiotherapy (SRT) or stereotactic radiosurgery (SRS) technology, which is used in the treatment of cancers [6,7]. SRS is an advanced surgical technique that precisely delivers radiation beams to specific points in the brain using a mask or frame and imaging techniques. This method is utilized for treating brain tumors, both benign and malignant, as well as certain other neurological conditions. On the other hand, SRT is a radiation therapy method that employs advanced technology to precisely target specific points in the body, including the brain, and can be used as a standalone method or as part of combination therapies [8–10]. These procedures use different technology -such as Gamma Knife technology, proton-based technologies, and accelerator technologies- to provide precise radiation to lesions and tumors [11].

Gamma Knife technology is one of the stereotactic technologies that utilize a gamma ray source. In this method, the gamma ray is directed to target points in the brain through a diaphragm that is able to move in three-dimensional coordinates. Gamma Knife technology is known as an effective

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Article highlights

- In this study, we focused on effective and new interventions.
- In this study, we covered several types of cancers.
- In this study, the most cost-effectiveness intervention was introduced by reviewed the literature.

method in the treatment of brain tumors and neurological diseases due to its high accuracy and very precise control of gamma rays [12]. Using a proton accelerator, proton-based technologies in stereotactic also produce high-energy protons and direct them to the target area in the brain or spine. This method is known as an effective surgical method in the treatment of cancerous tumors and neurological diseases due to its high accuracy and ability to penetrate more protons in the tissue [13,14]. Another method of stereotactic is linear accelerator technologies, in which a linear accelerator is used. Accelerators are very common and widely used in medicine. Approximately 30% of the world's accelerators are used for radiation therapy and 3% for nuclear medicine [15]. In radiation therapy, the use of linear electron accelerators with energies between 6 and 18 mega-electron volts is common. These accelerators can use either an electron beam or a photon beam generated from the collision of an electron beam for treatment purposes [16,17].

Although stereotactic technologies, as one of the most important innovations in cancer treatment, have been able to bring a significant improvement in the quality of life and treatment outcomes for many cancer patients, the use of these technologies, like any other technology, requires an acceptable level of cost. This study was designed to examine the available evidence on the cost-effectiveness of stereotactic technologies – Gamma Knife technology, proton-based technologies, and linear accelerator technologies – in the treatment of cancers.

The cost-effectiveness analysis of stereotactic technologies in the treatment of cancers not only helps us plan for the best use of financial resources in the field of public health but also assists health policymakers in making fundamental decisions in accordance with the needs of society about the improvement of the healthcare system.

2. Method

This systematic review aimed to evaluate economic evaluation of SRT/SRS technologies in the treatment of cancers. The review followed the approach outlined in the book 'Systematic Reviews to Support Evidence-Based Medicine' [18] and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19].

2.1. Search strategy

PubMed, Scopus, and Web of Science databases were searched from 30 December 1990 to 1 January 2023 using a combination of the following terms: Radiosurgery, Gamma Knife, Stereotactic, Linear Accelerator, LINAC, Cyber Knife,

Cost-Benefit Analysis, Cost-Effectiveness Analysis, Cost-utility Analysis, and economic evaluation. (The full search strategies is available as supplementary information).

2.2. Inclusion and exclusion criteria

All types of economic evaluation studies, including cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis, and cost-minimization analysis that utilized SRT/SRS technologies in the treatment of various cancers were included. Studies that were not available in full text or were not in English were excluded.

2.3. Selection/screening of studies

After removing duplicates, articles were screened based on their title and abstract. The full text of the included articles was then reviewed to ensure they met the inclusion criteria. All stages of selection and screening of articles were performed by two members of the research team. Two members of the research team conducted all stages of selection and screening, and disagreements were resolved through discussion or by a third person with more knowledge and experience. Endnote X5 resource management software was used for organizing, identifying duplicates, and screening studies. The PRISMA flow chart was used to report the results of the selection and screening process.

2.4. Quality assessment of the studies

In order to assess the quality of economic studies, the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement checklist was used. This checklist was developed in 2013 to ensure that health economic evaluations are identifiable, interpretable, and useful for decision-making. This checklist includes 28 questions categorized into seven general groups including title, abstract, introduction, methods, results, discussion, and other related information [20]. If the study met all the requirements of the checklist questions completely, a score of 1 was given. If they were partially met, a score of 0.5 was given, and otherwise, a score of zero was assigned. Therefore, a maximum score of 28 was included for the most complete report. In this study, the total scores assigned to each study were used to evaluate the quality of the studies. As such, the studies were classified into four categories: 1- excellent (≥ 24), 2- very good (20–23.5), 3- good (15.5–19.5), and 4- insufficient (≤ 15). The studies that received a score of less than 15.5 out of 28 were excluded from the study due to being in the fourth category.

2.5. Data extraction

Data extraction was performed independently by two reviewers using a researcher-made data extraction form. The form was pilot-tested on three articles, and improvements were made before extracting data from the remaining studies. Any ambiguities were resolved by consulting with other members of the research team. The extracted key fields encompassed the main characteristics of the studies and cost-

effectiveness findings. These main study characteristics included the first author, publication year, country, costing year, intervention, comparison arm, type of cancer, type of economic evaluation, outcome, perspective, time horizon, discount rate, sensitivity analysis, willingness to pay, and threshold. Additionally, the cost-effectiveness findings comprised the cost, effectiveness, and primary findings.

3. Results

A total of 3146 articles were identified by the search strategy. After removing duplicates, 2113 articles entered the screening stage. In the first phase of screening, based on the title and abstract, 1756 articles were excluded due to their irrelevance, and 357 articles remained for the second phase of screening. In the second phase of screening, based on the full text of the articles, 310 articles were excluded from the study, and finally, 47 articles that met the inclusion criteria were included and examined using a quality assessment checklist. The quality score of all the included studies using the CHEERS 2022 tool was above 15.5. Most of the studies received a score above 20 out of 28 and were therefore categorized as 'excellent' and 'very good' articles. Three studies received a score below 20 and fell into the third category, that is, 'good' articles (supplementary). Therefore, through qualitative appraisal, all 47 articles received an acceptable score and were included in the study (Figure 1).

3.1. Characteristics of the studies

From the 47 included articles, twenty-four studies have been conducted in the U.S.A., six studies in Canada, four studies in Taiwan, two studies in Australia, two studies in Germany, two studies in the Netherlands, and one study each in Japan, China, Brazil, England, France, Czech Republic, and Vietnam, respectively (Table 1).

Most of the studies conducted focused on the cost-effectiveness of linear accelerator technologies ($n = 39$), with a few related to the cost-effectiveness of Gamma Knife technology ($n = 4$) and proton-based technologies ($n = 4$). Among the included studies, the majority were related to lung cancer ($n = 13$), followed by prostate cancer ($n = 7$), liver and hepatocellular carcinoma ($n = 6$), head and neck cancer ($n = 2$), pancreatic cancer ($n = 2$), and kidney cancer ($n = 1$). The remaining studies were related to metastases, most of which were brain metastases (Figure 2).

Forty-one articles used cost-effectiveness analysis and six articles used cost-utility analysis. In most studies, a Markov model was used for economic evaluation ($n = 34$). The outcome was assessed in 33 studies using quality-adjusted life year (QALY), in 6 studies using LY, and in 8 studies using both QALY and LY. The most used perspective was the payer ($n = 27$), followed by the healthcare system perspective ($n = 8$) and the societal perspective ($n = 6$). The time horizon ranged from one year to 20 years (1, 2, 5, 10, 16, and 20 years) and from 20 years to a lifetime. Most studies used a discount rate of 3% ($n = 23$). The highest discount rate applied in the study was 5%, and

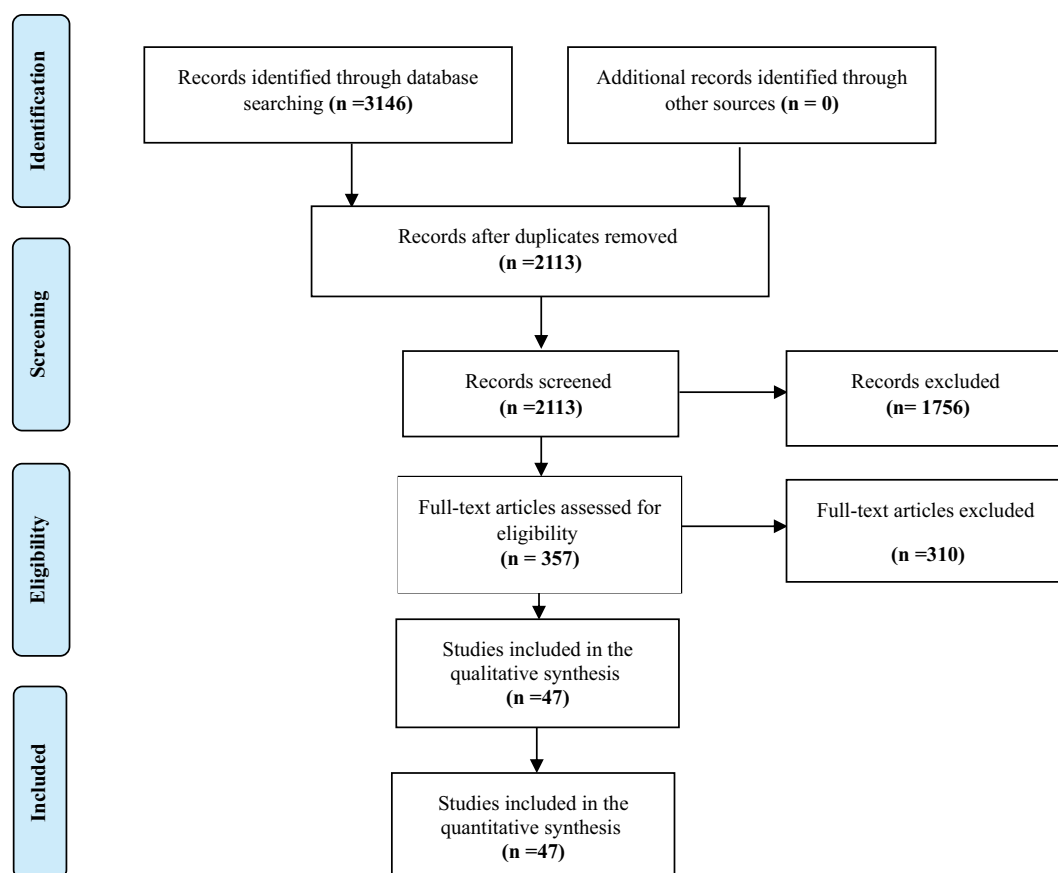


Figure 1. PRISMA flow chart for study selection.

Table 1. The main characteristics of studies.

First author (Publication year)	Country	Costing year	Intervention (Gamma Knife, Proton Therapy, Linear Accelerator)	Comparison arm	Type of cancer	Type of economic evaluation	Outcome	Perspective	Time horizon	Discount rate	sensitivity analysis	Willingness to pay threshold (USD**/QALY)
Wu et al. (2022) [21]	USA	2019	linear accelerator	1.Stereotactic body radiotherapy (SBRT) 2.microwave ablation (MWA)	lung cancer	CEA (Markov)	QALY	Payer perspective	5-year	3%	one -way, two-way, probabilistic sensitivity analyses	113271.25
Okazaki et al. (2022) [22]	Japan	NA*	linear accelerator	1.carbon-ion radiotherapy 2.stereotactic body radiotherapy (SBRT)	lung cancer	CEA (Markov)	QALY & LY	NA	NA	NA	one-way and probabilistic sensitivity	27611.82 and 55,226.31
Lourenco et al. (2022) [23]	Australia	2020	linear accelerator	1.single-fraction (SF) stereotactic Ablative radiotherapy (SABR) 2.Multi-fraction (MF) stereotactic Ablative radiotherapy (SABR)	Pulmonary Oligometastases	CEA (partitioned survival model (PSM))	QALY	societal perspective	10-year	5%	deterministic and probabilistic sensitivity analyses	36282.09
Li et al. (2022) [24]	China	2021	Proton	1.photon SBRT 2. Proton SBRT	localized prostate cancer	CEA (Markov)	QALY	societal perspective	NA	3%	Probabilistic sensitivity analysis	40290.72
Donovan et al. (2022) [25]	Canada	2020	linear accelerator	1.radiofrequency ablation (RFA) 2.Stereotactic Body Radiotherapy (SBRT)	Early-Stage Renal Cell Carcinoma	CEA (Markov)	QALY	Payer perspective	5-year	1.5%	One-way sensitivity analysis	between 40732.09– 81464.90
Arruda et al. (2022) [26]	Brazil	2021	linear accelerator	1.stereotactic body radiotherapy (SBRT) 2.conventional radiotherapy	lung cancer	CEA (Markov)	QALY & LY	Healthcare System perspective	lifetime	5%	one-way and probabilistic sensitivity	10573.65
Raymakers et al. (2021) [27]	Canada	2018	linear accelerator	1.stereotactic Ablative radiotherapy (SABR) 2.standard care (SC)	oligometastatic disease	CEA (Markov)	QALY & LY	Payer perspective	lifetime	%1/5	probabilistic sensitivity	between 42003.82– 84008.39
Mehrens et al. (2021) [28]	Germany	2019	linear accelerator	1.stereotactic ablative radiotherapy (SABR) 2.standard care (SC)	oligometastatic disease	CEA (partitioned survival model (PSM))	QALY	health care perspective	16-year	3%	Deterministic and probabilistic sensitivity	113271.25

(Continued)

Table 1. (Continued).

First author (Publication year)	Country	Costing year	Intervention (Gamma Knife, Proton Therapy, Linear Accelerator)	Comparison arm	Type of cancer	Type of economic evaluation	Outcome	Perspective	Time horizon	Discount rate	sensitivity analysis	Willingness to pay threshold (USD**/QALY)
Leung et al. (2021) [29]	Taiwan	2020	linear accelerator	1.Stereotactic body radiotherapy (SBRT) plus cetuximab 2.Stereotactic body radiotherapy (SBRT) alone	head and neck cancer	CUA (Markov)	QALY	health payer perspective	5- year and 10-year	3%	one-way and probabilistic sensitivity	173861.02
Jin et al. (2021) [30]	UK	2016	linear accelerator	1.stereotactic ablative radiotherapy (SABR) 2.Surgery and Radiofrequency Ablation	Liver Cancer and Hepatocellular Carcinoma	CEA (Markov)	QALY	NHS and Personal Social Services perspective.	lifetime	3.5%	one-way and probabilistic sensitivity	33986.50
Alvamani et al. (2021) [31]	Canada	2018	linear accelerator	1.LDR-b 2.HDR-b 3. hFIMRT 4.HDR- IMRT 5.cfIMRT 6. SBRT	prostate cancer	CUA (Markov)	QALY	health care system perspective	NA	1.5%	probabilistic sensitivity	42003.82
Wolff et al. (2020) [32]	Netherlands	2018	linear accelerator	1.stereotactic body radiotherapy (SBRT) 2.video assisted thoracic surgery	lung cancer	CEA (microsimulation model)	QALY	health care perspective	NA	1.5%	deterministic and probabilistic sensitivity	72290.79
Tran et al. (2020) [33]	Australia	2017	linear accelerator	1.whole-brain radiotherapy (WBRT) 2.hippocampal- avoidant WBRT (HA-WBRT) 3.Stereotactic Radiosurgery (SRS) or Surgery Alone	Brain Metastases	CEA (Markov)	QALY & LY	healthcare provider	20-year	5%	Probabilistic sensitivity	42026.01
Kumar et al. (2020) [34]	USA	2019	linear accelerator	1.Stereotactic Ablative Radiotherapy (SABR) 2.standard therapy	Oligometastatic Cancer	CEA (Markov)	QALY	health care sector and societal perspectives	lifetime	3%	One-way and probabilistic sensitivity analyses	113271.25
Kim et al. (2019) [35]	USA	2018	linear accelerator	1.SBRT plus maintenance therapy 2.maintenance therapy alone	lung cancer	CEA (Markov)	QALY	Payer perspective	10-year	3%	One-way and probabilistic sensitivity	115302.84

(Continued)

Table 1. (Continued).

First author (Publication year)	Country	Costing year	Intervention (Gamma Knife, Proton Therapy, Linear Accelerator)	Comparison arm	Type of cancer	Type of economic evaluation	Outcome	Perspective	Time horizon	Discount rate	sensitivity analysis	Willingness to pay threshold (USD**/QALY)
Parikh et al. (2018) [36]	USA	2016	linear accelerator	1.stereotactic body radiotherapy (SBRT) 2.radiofrequency ablation (RFA)	early-stage hepatocellular carcinoma	CEA (NA)	LY	Medicare perspective	NA	NA	2-way sensitivity	120317.76 per life-year
Paix et al. (2018) [37]	France	2017	linear accelerator	1.stereotactic body radiotherapy (SBRT) 2.surgery for medically operable early- stage non-small cell	lung cancer	CEA (Markov)	QALY	payer perspective	NA	4%	.Deterministic (DSA) and probabilistic (PSA) sensitivity	42234.14and \140780.47
Kim et al. (2018) [38]	USA	2016	linear accelerator	1.platinum-based chemotherapy alone 2.chemotherapy plus cetuximab 3.stereotactic body radiotherapy (SBRT) alone 4.SBRT plus cetuximab 5.intensity modulated radiotherapy (IMRT) plus chemotherapy 6.no treatment strategy	recurrent squamous cell carcinoma of the head and neck	CEA (Markov)	QALY	Payer perspective	NA	3%	One-way and probabilistic sensitivity	120317.76
Horáková et al. (2018) [39]	Czech Republic	NA	linear accelerator	1.Robotic stereotactic body radiotherapy (rSBRT) 2.intensity- modulated radiation therapy (IMRT)	localized prostate cancer	CUA (NA)	QALY	provider's perspective	10-year	3%	NA	NA
Pollom et al. (2017) [40]	USA	2015	linear accelerator	1.stereotactic body radiotherapy (SBRT) 2.radiofrequency ablation (RFA)	inoperable localized hepatocellular carcinoma (HCC)	CEA (Markov)	QALY	societal perspective	NA	3%	Deterministic and probabilistic sensitivity	121523.34

(Continued)



Table 1. (Continued).

First author (Publication year)	Country	Costing year	Intervention (Gamma Knife, Proton Therapy, Linear Accelerator)	Comparison arm	Type of cancer	Type of economic evaluation	Outcome	Perspective	Time horizon	Discount rate	sensitivity analysis	Willingness to pay threshold (USD**/QALY)
Leung et al. (2017) [41]	Taiwan	NA	proton	1.stereotactic body radiotherapy (SBRT) 2.proton beam therapy	inoperable advanced hepatocellular carcinoma	CUA (Markov)	QALY	NA	5-year	3%	One-way and probabilistic sensitivity	166929.70
Kim et al. (2017) [42]	USA	2016	linear accelerator	1.Stereotactic Radiotherapy (SRS)Alone 2.Stereotactic Radiotherapy (SRS) with Upfront WBRT	Brain Metastases	CEA (Markov)	QALY	Payer perspective	NA	3%	One-way and probabilistic sensitivity	120317.76
Helou et al. (2017) [43]	Canada	2015	linear accelerator	1.Stereotactic Body Radiotherapy (SBRT) 2.Low Dose Rate Brachytherapy (LDR-BT)	Prostate Cancer	CUA (Markov)	QALY & LY	Payer perspective	lifetime	5%	One- and two-way deterministic sensitivity	51536.39
Wernicke et al. (2016) [44]	USA	NA	linear accelerator	1.surgical resection and cesium-131 intraoperative brachytherapy 2.surgical resection and Stereotactic Radiotherapy (SRS)	Brain Metastases	CEA (NA)	QALY	NA	NA	NA	NA	60761.67
Leung et al. (2016) [45]	Taiwan	2015	linear accelerator	1.Stereotactic body radiotherapy (SBRT) 2.sorafenib	unresectable advanced hepatocellular carcinoma	CEA (Markov)	QALY & LY	National Health Insurance (NHI) in Taiwan	5- year	3%	One-way sensitivity The probabilistic sensitivity	172560.15
Leung et al. (2016) [46]	Taiwan	2015	linear accelerator	1.gemcitabine plus intensity- modulated radiotherapy (Gem-IMRT) 2.gemcitabine alone 3.gemcitabine plus stereotactic body radiotherapy (gem-SBRT)	pancreatic cancer	CEA (Markov)	QALY	National Health Insurance (NHI)	5-year	3%	One-way sensitivity The probabilistic sensitivity	157637.75

(Continued)

Table 1. (Continued).

First author (Publication year)	Country	Costing year	Intervention (Gamma Knife, Proton Therapy, Linear Accelerator)	Comparison arm	Type of cancer	Type of economic evaluation	Outcome	Perspective	Time horizon	Discount rate	sensitivity analysis	Willingness to pay threshold (USD**/QALY)
Lester-Coll et al. (2016) [47]	USA	2015	linear accelerator	1.stereotactic body radiotherapy (SBRT) 2.video-assisted thoracic surgery (VATS) wedge resection 3.Systemic Therapy	Pulmonary Oligometastases	CEA (Markov)	QALY	NA	5-year	3%	One-way sensitivity analyses and probabilistic sensitivity	121523.34
Lester-Coll et al. (2016) [48]	USA	2015	Gamma Knife	1.stereotactic radiosurgery (SRS) 2.whole-brain radiation therapy (WBRT) 3.SRS+WBRT	brain metastases	CEA (Markov)	QALY	US third-party payer perspective	24- month	3%	One-way sensitivity analyses and probabilistic sensitivity	121523.34
Kim et al. (2016) [49]	USA	2014	linear accelerator	1.stereotactic body radiotherapy (SBRT) 2. Radiofrequency Ablation	Colorectal Liver Metastases	CEA (Markov)	QALY	Payer perspective	lifetime	3%	One-way and probabilistic sensitivity	122739.11
Smith et al. (2015) [50]	USA	NA	linear accelerator	1.stereotactic ablative radiotherapy (SABR) 2.Sublobar resection 3.lobectomy	Lung cancer	CEA (NA)	LY	Payer perspective	NA	NA	NA	61369.56, 122739.11, and 245,478.23
Savitz et al. (2015) [51]	USA	2014	linear accelerator	1.stereotactic radiosurgery (SRS) 2.whole-brain radiotherapy [WBRT] 3.hippocampal avoidance WBRT [HA-WBRT] 4.SRS plus WBRT 5. SRS plus HA- WBRT	Brain Metastases	CEA (Markov)	QALY	payer's (Medicare) perspective	NA	3%	deterministic and probabilistic	122739.11
Kim et al. (2015) [52]	USA	2014	linear accelerator	1.stereotactic body radiotherapy (SBRT) 2.external beam radiotherapy	Vertebral Bone Metastases	CEA (Markov)	QALY	Payer perspective	lifetime	3%	1-way, 2-way and probabilistic sensitivity	122739.11

(Continued)

Table 1. (Continued).

First author (Publication year)	Country	Costing year	Intervention (Gamma Knife, Proton Therapy, Linear Accelerator)	Comparison arm	Type of cancer	Type of economic evaluation	Outcome	Perspective	Time horizon	Discount rate	sensitivity analysis deterministic and probabilistic sensitivity	Willingness to pay threshold (USD**/QALY)
Sher et al. (2014) [53]	USA	2014	linear accelerator	1.Stereotactic body radiotherapy (SBRT) 2.Intensity- modulated radiation therapy (IMRT)	Prostate Cancer	CEA (Markov)	QALY	payer perspective	lifetime	3%	deterministic and probabilistic sensitivity	over 122,739.11
Mitera et al. (2014) [54]	Canada	2010	linear accelerator	1.Conventionally fractionated radiotherapy (CFRT) 2.Stereotactic body radiotherapy (SBRT)	non – small-cell lung cancer (NSCL)	CEA (NA)	LY	public payer perspective	NA	NA	One- and two-way sensitivity	55360.76
Louie et al. (2014) [55]	Canada	2013	linear accelerator	1.Stereotactic ablative radiotherapy (SABR) 2. Conventional Radiotherapy 3.Best supportive care 4.Sublobar resection 5.Lobectomy 6. Pneumonectomy	Stage I Non-Small Cell Lung Cancer	CEA (Cancer Risk Management Model (CRMM))	QALY	health care payer perspective	10-year	3%	one-way sensitivity probabilistic sensitivity	104155.80
Hall et al. (2014) [56]	USA	2014	Gamma Knife	1.stereotactic radiosurgery (SRS) alone 2.SRS+ whole- brain radiotherapy (WBRT) 3.surgery followed by SRS	brain metastases	CEA (NA)	LY	payer perspective	NA	NA	NA	NA
Vuong et al. (2013) [57]	Germany	NA	Gamma Knife	1.Stereotactic radiosurgery (SRS) 2.surgical resection	brain metastases	CEA (NA)	LY	Payer perspective	NA	No discounted rate	NA	NA

(Continued)

Table 1. (Continued).

First author (Publication year)	Country	Costing year	Intervention (Gamma Knife, Proton Therapy, Linear Accelerator)	Comparison arm	Type of cancer	Type of economic evaluation	Outcome	Perspective	Time horizon	Discount rate	sensitivity analysis	Willingness to pay threshold (USD**/QALY)
Shah et al. (2013) [58]	USA	2012	linear accelerator	1.SBRT in marginally operable 2.SBRT in clearly operable 3.wedge resection 4.lobectomy	Stage I Non-Small Cell Lung Cancer	CEA (Markov)	QALY	payer (Medicare) perspective	NA	3%	One-Way Sensitivity Analyses Two-Way Sensitivity Analysis Probabilistic Sensitivity Analysis probabilistic sensitivity	more than 636,120
Lincy et al. (2012) [59]	USA	2007	linear accelerator	1.stereotactic radiosurgery (SRS) + Whole Brain Radiation Therapy (WBRT) 2.stereotactic radiosurgery (SRS) + observation	Brain Metastases	CEA (Decision-tree model)	QALY & LY	Perspective of Patients and Families	10-year, 5-year, and 1-year	NA	One-way sensitivity analyses	137328.64
Vuong et al. (2012) [60]	Vietnam	2008	Gamma Knife	1.Stereotactic Radiosurgery (SRS) 2.Surgical Resection	Brain Metastasis	CEA (NA)	LY	Payer perspective	NA	NA	bootstrap method	NA
Puri et al. (2012) [61]	USA	2010	linear accelerator	1.Stereotactic body radiotherapy (SBRT) 2.surgical intervention	lung cancer	CEA (Markov)	QALY & LY	Payer perspective Societal perspective	NA	NA	One and 2-way sensitivity probabilistic sensitivity analysis	95253.29 per life year gained
Parthan et al. (2012) [62]	USA	2011	proton	1.Stereotactic body radiotherapy (SBRT) 2.intensity- modulated radiation therapy (IMRT) 3.proton beam therapy (PT)	prostate cancer	CEA (Markov)	QALY	health care payer as well as a societal perspective	Lifetime	3.0%	One-way and probabilistic sensitivity	64801.76

(Continued)

Table 1. (Continued).

First author (Publication year)	Country	Costing year	Intervention (Gamma Knife, Proton Therapy, Linear Accelerator)	Comparison arm	Type of cancer	Type of economic evaluation	Outcome	Perspective	Time horizon	Discount rate	sensitivity analysis	Willingness to pay threshold (USD**/QALY)
Murphy et al. (2012) [63]	USA	2009	linear accelerator	1.gemcitabine alone (gem- alone) 2.gemcitabine plus conventional radiotherapy (gem-RT) 3.gemcitabine plus intensity- modulated radiotherapy (gem-IMRT) 4.gemcitabine with stereotactic body radiotherapy (gem-SBRT)	Locally Advanced Pancreatic Cancer	CEA (Markov)	QALY	Payer perspective	5-year	3%	One-way and probabilistic sensitivity analysis	66943.09
Hodges et al. (2012) [64]	USA	2010	linear accelerator	1.Stereotactic body radiotherapy (SBRT) 2.intensity- modulated radiation therapy (IMRT)	Organ-Confined Prostate Cancer	CEA (Markov)	QALY	payer perspective	10-year	3%	One- and two-way & Monte Carlo simulation with second-order probabilistic sensitivity analysis	66148.12
Sher et al. (2011) [65]	USA	2009	linear accelerator	1.Stereotactic body radiotherapy (SBRT) 2. Radiofrequency ablation (RFA) 3.three- dimensional conformal radiation therapy (3D- CRT)	medically inoperable, early-stage non – small cell lung cancer	CEA (Markov)	QALY	payer perspective	5-year	3%	one-way and two-way sensitivity analysis	NA

(Continued)

Table 1. (Continued).

First author (Publication year)	Country	Costing year	Intervention (Gamma Knife, Proton Therapy, Linear Accelerator)	Comparison arm	Type of cancer	Type of economic evaluation	Outcome	Perspective	Time horizon	Discount rate	sensitivity analysis	Willingness to pay threshold (USD**/QALY)
Grutters et al. (2010) [66]	Netherlands	2007	protons	1. carbon-ions therapy 2. protons therapy 3. conventional radiotherapy (CRT) 4. Stereotactic body radiotherapy (SBRT)	non-small cell lung cancer	CEA (Markov)	QALY	health-care perspective	5-year	4%	probabilistic sensitivity analysis	129.73
Papatheofanis et al. (2009) [67]	USA	2006	linear accelerator	1. CyberKnife stereotactic radiosurgery (SRS) 2. external beam radiation therapy (EBRT)	Metastatic spinal tumors	CUA (Markov)	QALY	payer perspective	12-month	NA	multiple post-hoc sensitivity and secondary analyses	141040.30

NA: not applicable. CEA: cost-effectiveness analysis. CUA: cost-utility analysis. QALY: quality-adjusted life year. LY: life year gained. *For unspecified costing years, a year before publication was used. **2022 USD.

the lowest discount rate applied was 1.5%. More than 30 studies had used probabilistic sensitivity analysis, and deterministic sensitivity analysis had been used in only a few studies. Furthermore, sensitivity analysis in most studies was one-way, and in some studies, two-way sensitivity analysis had also been used. The willingness-to-pay threshold also varied in different studies, and in most studies, a willingness-to-pay threshold of USD100,000 per QALY was considered ($n = 21$) (Table 1).

3.2. Cost-effectiveness findings

Table 2 displays the cost-effectiveness findings of SRS/SRT technologies, including linear accelerator, Gamma Knife, and proton-based technologies. It should be noted that all cost-effectiveness results reported in this study were extracted directly from the source papers and have been presented as reported therein. Standardization based on a common currency and time basis was not performed. Therefore, the reported findings reflect the original presentation in the literature.

3.2.1. Linear accelerator

Out of the included studies, 39 studies were related to linear accelerator SRT/SRS technology (39 out of 47), with most of them focusing on the cost-effectiveness of this technology for lung cancer (12 out of 39), followed by prostate cancer (5 out of 39), and liver cancer and hepatocellular carcinoma (5 out of 39).

3.2.1.1. Cost-effectiveness of linear accelerator radiosurgery technology in lung cancer. According to the findings of the studies, SRT is considered a cost-effective option than conventional fractionated radiotherapy (CFRT) [26,54,55], three-dimensional conformal radiotherapy (3D-CRT), radiofrequency ablation (RFA) [65], video-assisted thoracic surgery (VATS) [32], surgery [50,61], and lobectomy [37] for stage I non-small cell lung cancer (NSCLC). However, results regarding lobectomy are contradictory in some studies. Two studies have shown that SRT is not cost-effective compared to lobectomy for stage I NSCLC, and lobectomy may be a cost-effective option [50,55]. In other studies, it has been shown that for patients with marginally operable stage I NSCLC, SRT is the dominant strategy and, therefore, cost-effective, yet for patients who are clearly operable, lobectomy is a cost-effective treatment option [58]. In a few studies, there have been options more cost-effective than SRT, such as microwave ablation (MWA) in one study and carbon ion radiotherapy in another study [21,22]. In another study, it has been shown that adding SRT to maintenance therapy compared to maintenance therapy alone is not cost-effective, and it is only close to being cost-effective in some cases [35].

3.2.1.2. Cost-effectiveness of linear accelerator radiosurgery technology in prostate cancer. SRT is considered a cost-effective radiotherapy procedure in the treatment of intermediate-risk prostate cancer compared to fractionated intensity-modulated radiotherapy (IMRT), IMRT with high-dose-rate brachytherapy (HDR-BT), and monotherapy with high-dose-rate brachytherapy [31]. SRT is also a cost-effective

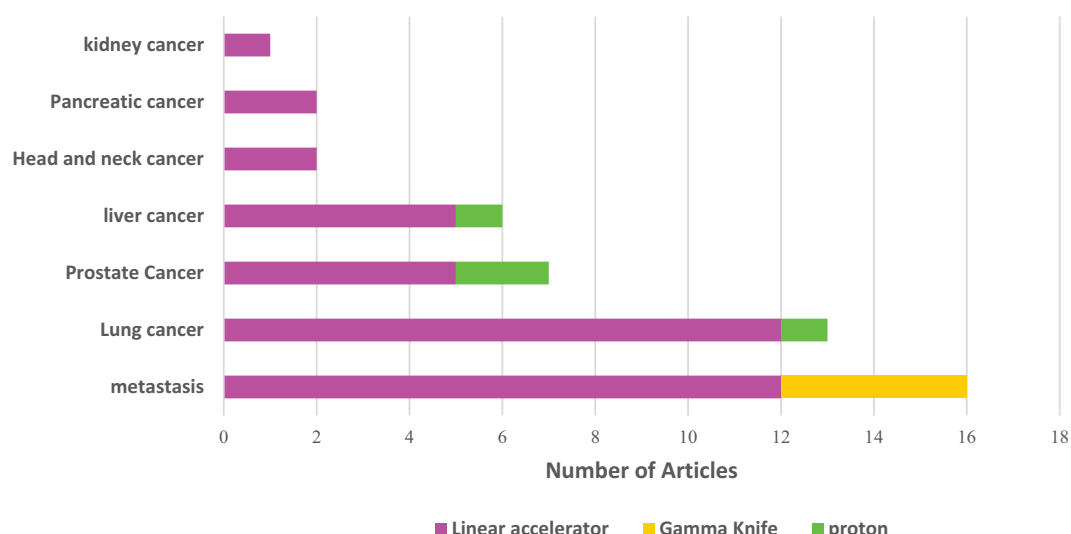


Figure 2. Number of articles on stereotactic radiosurgery technologies for cancers.

strategy for the treatment of localized and low-risk prostate cancer compared to low-dose-rate brachytherapy (LDR-BT) [43]. Regarding IMRT, in addition to the above study, two other studies have also shown that SRT is a cost-effective treatment strategy for low- to intermediate-risk prostate cancer compared to IMRT [53,64]. However, a study showed that IMRT is both more effective and less expensive than robotic SRT for the treatment of localized prostate cancer [39].

3.2.1.3. Cost-effectiveness of linear accelerator radiosurgery technology in liver cancer. SRT is a cost-effective option compared to surgery and RFA for patients with oligo metastases and hepatocellular carcinoma [30]. SRT is also a cost-effective option compared to sorafenib for advanced liver cancer [45]. Regarding RFA, the results were different in various studies. In one study, it was found that SRT was not cost-effective for the primary treatment of inoperable and localized hepatocellular carcinoma [40]. Moreover, SRT was not a cost-effective treatment option compared to RFA for colorectal liver metastases that are not amenable to surgery [49]. In another study, RFA was not significantly different from SRT in terms of survival, hospitalization, or costs for early-stage hepatocellular carcinoma [36].

3.2.1.4. Cost-effectiveness of linear accelerator radiosurgery technology in head and neck cancer. For the treatment of head and neck cancer, SRT was found to be a cost-effective treatment option compared to platinum-based chemotherapy alone, chemotherapy with cetuximab, SRT with cetuximab, and IMRT with chemotherapy. After SRT, the combination of SRT with cetuximab was identified as a cost-effective strategy [38]. SRT with cetuximab was also found to be a cost-effective option than SRT alone for recurrent squamous cell carcinoma of the head and neck that had previously been irradiated [29].

3.2.1.5. Cost-effectiveness of linear accelerator radiosurgery technology in pancreatic cancer. Combining gemcitabine with SRT increases clinical effectiveness beyond

gemcitabine alone with costs that are acceptable [63]. Another study found that gemcitabine with modern radiotherapy (gem-IMRT) and gemcitabine with SRT are not cost-effective for advanced pancreatic cancer [46].

3.2.1.6. Cost-effectiveness of linear accelerator radiosurgery technology in kidney cancer. For early-stage renal cell carcinoma, SRT was shown to be economically superior to RFA. In patients with small tumors, SRT was more effective and slightly more expensive than RFA. However, for larger tumors, SRT was less expensive and more effective than RFA [25].

3.2.2. Gamma Knife

Among the studies included in the current research, four cases investigated the cost-effectiveness of SRS based on Gamma Knife technology, all of which were related to brain metastasis. In one study, SRS alone emerged as a cost-effective strategy for patients with brain metastases compared to SRS with whole-brain radiotherapy (WBRT). SRS alone may also be cost-effective compared to WBRT alone, but this depends on willingness to pay, cost of SRS, and patient preferences [48]. Another study showed that SRS alone provides cost-effective care than SRS with WBRT [56]. Regarding tumor removal surgery (RS), findings showed that SRS is more effective and less costly than RS [57]. In another study, the cost per year of life gained for RS was higher than that for SRS [60].

3.2.3. Proton-based technology

Among all the studies on SRT included in the present research, only four studies examined proton-based technology as one of the comparison options. One study examined the cost-effectiveness of this technology for lung cancer, two studies for prostate cancer, and one study for liver cancer.

3.2.3.1. Cost-effectiveness of proton-based technology in Lung cancer. Only one study assessed the cost-effectiveness of proton therapy and SRT for lung cancer. The results of this study showed that for inoperable non-small cell lung cancer, SRT and

Table 2. The main result of studies.

First author (Publication year)	Treatment options	Effectiveness			Cost*	Main finding
		QALY	LY			
Wu et al (2022) [21]	stereotactic body radiotherapy (SBRT)	2.33	-		255167.27	The ICER* was \$1677090.67/QALY, indicating that MWA is the more cost-effective strategy.
Okazaki et al (2022) [22]	microwave ablation (MWA)	2.31	-		221253.86	
Okazaki et al (2022) [22]	Carbon-ion radiotherapy (CIRT)	-	-		-	Carbon-ion radiotherapy is a cost-effective treatment approach
Liou et al (2022) [23]	stereotactic body radiotherapy (SBRT)	-	-		-	
Liou et al (2022) [23]	single-fraction (SF) SABR	2.43	3.24		32893.77	The within-trial economic evaluation produced an ICER of \$12509.31/QALY, whereas the extrapolated analysis resulted in an ICER of \$18395.11/QALY.
Liou et al (2022) [23]	multifraction (MF) SABR	2.25	2.99		30650.62	
Liou et al (2022) [23]	single-fraction (SF) SABR	4.48	6.05		2243.15	
Li et al (2022) [24]	multifraction (MF) SABR	3.10	4.13		2243.15	The ICER ratio for protons was \$50780.99/QALY. Protons was cost-effective for patients ≤62-year-old at the WTP of China.
Li et al (2022) [24]	Proton Stereotactic body radiation therapy (SBRT)	-	-		-	
Li et al (2022) [24]	photon Stereotactic body radiation therapy (SBRT)	-	-		-	
Donovan et al (2022) [25]	radiofrequency ablation (RFA)	3.607	-		17600.33	SBRT economically dominated RFA with a gain of 4.103 QALYs and a cost of \$15461.28, compared with 3.607 QALYs at a cost of \$17600.33 for RFA. The ICER was 4312.68 for SBRT in the base case analysis (BCE). In patients with small tumors (T1a), SBRT compared with RFA was more effective and marginally more costly, resulting in an ICER of \$2119.84/QALY, while for larger tumors (T1b), SBRT was less costly and more effective than RFA, resulting in an ICER of - 21999.46
Donovan et al (2022) [25]	Stereotactic Body Radiotherapy (SBRT)	4.109	-		15461.28	
Donovan et al (2022) [25]	radiofrequency ablation (RFA)	3.641	-		13389.47	
Donovan et al (2022) [25]	Stereotactic Body Radiotherapy (SBRT)	4.119	-		14400.88	
Donovan et al (2022) [25]	radiofrequency ablation (RFA)	3.459	-		35948.90	
Donovan et al (2022) [25]	Stereotactic Body Radiotherapy (SBRT)	4.067	-		18484.96	
Arruda et al (2022) [26]	stereotactic body radiotherapy (SBRT)	2.59	3.25		13932.37	SBRT was more cost-effective than CFRT for NSCLC in a public health system of an upper-middle-income country.
Arruda et al (2022) [26]	conventional fractionated radiotherapy (CFRT)	2.00	4.17		13827.95	
Arruda et al (2022) [26]	stereotactic radiotherapy (SABR)	1.88	-		571732.60	
Raymakers et al (2021) [27]	standard care (SC)	1.03	-		527354.84	results suggest that the cost-effectiveness of SABR is contingent on the uncertainty in the evidence base.
Raymakers et al (2021) [27]	stereotactic ablative radiation (SABR)	0.78	-		456356.26	
Raymakers et al (2021) [27]	standard care (SC)	1.34	-		397251.32	
Mehrens et al (2021) [28]	stereotactic body radiotherapy (SBRT) plus cetuximab	12.27	-		355629.09	local treatment with SABR adds QALYs for patients with certain oligo metastatic cancers and represents an intermediate- and long-term cost-effective treatment strategy.
Leung et al (2021) [29]	stereotactic body radiotherapy (SBRT) alone	9.29	-		162083.55	SBRT+Cet was cost-effective and benefited patients with previously irradiated rSCCHN.
Jin et al (2021) [30]	Stereotactic Ablative Radiation Therapy (SABR)	2.5601	-		28655.72	SABR to be cost-effective for patients with liver oligo metastases and HCC.
Jin et al (2021) [30]	Surgery and Radiofrequency Ablation	2.2848	-		37211.82	
Jin et al (2021) [30]	stereotactic body radiotherapy (SBRT)	11.38	-		11585.63	
Alvamani et al (2021) [31]	Conventionally fractionated IMRT	10.59	-		22948.72	Stereotactic body radiotherapy is the most cost-effective radiation treatment modality in treatment of intermediate-risk prostate cancer
Alvamani et al (2021) [31]	hypo fractionated IMRT	10.86	-		16525.20	
Alvamani et al (2021) [31]	IMRT combined with high-dose-rate (HDR) brachytherapy	9.95	-		19531.15	
Wolff et al (2020) [32]	HDR brachytherapy monotherapy	10.63	-		10592.87	SBRT is slightly more effective (0.05 QALYs), and less expensive (-11703.88) than VATS.
Wolff et al (2020) [32]	low-dose-rate brachytherapy monotherapy	11.00	-		10308.07	
Wolff et al (2020) [32]	stereotactic body radiotherapy (SBRT)	5.86	-		30615.15	
Tran et al (2020) [33]	video assisted thoracic surgery (VATS)	5.81	-		42317.58	HA-WBRT may be cost-effective for the treatment of melanoma brain metastases.
Tran et al (2020) [33]	whole-brain radiotherapy (WBRT)	1.74	2.38		47380.90	
Tran et al (2020) [33]	hippocampal-avoidant WBRT (HA-WBRT)	1.88	2.38		50744.84	
Tran et al (2020) [33]	Stereotactic Radiosurgery (SRS)/Surgery Alone	1.65	2.13		54646.02	

(Continued)

Table 2. (Continued).

First author (Publication year)	Effectiveness				Main finding
	Treatment options	QALY	LY	Cost*	
Kumar et al. (2020) [34]	Stereotactic Ablative Radiotherapy (SABR) health care sector perspective	4.84	-	521230.10	The addition of SABR increased total costs by \$61460.98 (health care sector) or \$82460.33 (societal) and improved effectiveness by 1.88 QALYs compared with standard therapy, leading to an ICER of \$32742.19/QALY (health care sector) or \$43929.99/QALY (societal). SABR was the cost-effective treatment option 99.8% (health care sector) or 98.7% (societal) of the time.
	Standard therapy	2.96	-	459769.12	
	Stereotactic Ablative Radiotherapy (SABR) societal perspective	4.84	-	617716.81	
	Standard therapy	2.96	-	535256.48	
Kim et al (2019) [35]	SBRT plus maintenance therapy	-	-	-	ICER of \$650522.49 per QALY gained for the EGFR or ALK-positive group. ICER of \$345041.45 per QALY gained for the PDL-1-positive group; Thus, adding SBRT to maintenance therapy for either of these groups was not cost-effective with a WTP threshold of \$115302.84/QALY gained. ICER of \$148076.52 per QALY gained for mutation-negative cohort. Thus, SBRT plus maintenance therapy was close to being cost-effective with a WTP threshold of \$115302.84/QALY gained.
	EGFR/ALK mutation positive cohort	-	-	-	
	PDL-1-positive cohort	-	-	-	
	SBRT plus maintenance therapy	-	-	-	
Parikh et al (2018) [36]	Maintenance therapy alone	-	-	-	RFA vs SBRT resulted in no significant difference in survival, 90-day hospitalization, or costs.
	Mutation-negative cohort	-	-	-	
	Stereotactic body radiotherapy (SBRT)	-	-	62259.63	
	radiofrequency ablation (RFA)	-	-	102289.35	
Paix et al (2018) [37]	SBRT plus maintenance therapy	16.35	-	12999.88	SBRT is dominant over lobectomy in operable early-stage NSCLC treatment.
	SBRT	15.80	-	11304.67	
	surgery for medically operable early stage non-small cell	-	-	-	
	platinum-based chemotherapy alone	-	-	-	
Kim et al (2018) [38]	chemotherapy plus cetuximab	-	-	-	The most cost-effective therapy was SBRT alone with \$181518.59 per QALY gained. If median survival of SBRT alone was ≥ 11 months, SBRT was considered to be cost-effective. The second most effective one was SBRT plus cetuximab with an ICER of 264108.32 per QALY gained. In addition, IMRT plus chemotherapy was absolutely dominated. Chemotherapy plus cetuximab (current standard of care) was the least cost-effective therapy among all other therapies.
	Stereotactic body radiotherapy (SBRT) alone	-	-	-	
	SBRT plus cetuximab	-	-	-	
	intensity modulated radiotherapy (IMRT) plus chemotherapy	-	-	-	
Horakova et al (2018) [39]	no treatment strategy	-	-	-	In realistic scenario, rSBRT was more costly than IMRT (\$7538.43 vs. \$5126.31 per patient). In other considered scenarios, rSBRT was also more expensive than IMRT (\$4990.08 vs. \$3931.47 for optimistic and \$10780.14 vs. \$7195.62 for pessimistic scenarios). In every scenario concerned IMRT was both more effective and less costly than rSBRT. Namely, in realistic scenario, IMRT and rSBRT accrued 9.96 QALY/\$ 9152.72 and 9.93 QALY/\$5015.63, respectively.
	Robotic stereotactic body radiotherapy (rSBRT)	9.93	-	4990.08	
	Optimistic intensity-modulated	9.96	-	3931.47	
	radiation therapy (IMRT)	9.93	-	7538.43	
Pollom et al (2017) [40]	Robotic stereotactic body radiotherapy (rSBRT)	9.96	-	5126.31	SBRT for initial treatment of localized, inoperable HCC is not cost-effective. SBRT is the preferred salvage therapy for local progression after RFA.
	intensity-modulated	9.96	-	10780.14	
	radiation therapy (IMRT)	9.93	-	7195.62	
	Robotic stereotactic body radiotherapy (rSBRT)	9.96	-	240077.86	
Leung et al (2017) [41]	radiation therapy (IMRT)	1.565	-	234890.03	PT is a cost-effective therapy for inoperable advanced hepatocellular carcinoma at the willingness-to-pay threshold of Taiwan.
	radiofrequency ablation (RFA)	1.558	-	16511.23	
	Stereotactic body radiotherapy (SBRT)	NA	-	43175.81	
	proton beam therapy (PT)	2.61	NA	11931.91	
Kim et al (2017) [42]	Stereotactic Radiosurgery (SRS) Alone	NA	NA	-	results were most sensitive to variation in cognitive decline rates for both groups and median survival rates, but the SRS alone remained cost-effective for most parameter ranges
	Stereotactic Radiosurgery (SRS) with Upfront WBRT	NA	NA	-	
	Stereotactic Body Radiotherapy (SBRT)	9.888	11.166	74876.19	
	Low Dose Rate Brachytherapy (LDR-BT)	9.897	11.166	77297.37	
Helou et al (2017) [43]	Stereotactic Body Radiotherapy (SBRT)	9.888	11.166	74876.19	SBRT represents an economically attractive radiation strategy.

(Continued)

Table 2. (Continued).

First author (Publication year)	Effectiveness				Main finding
	Treatment options	QALY	LY	Cost*	
Wernicke (2016) [44]	surgical resection (S) and Cesium-131 (Cs-131)	0.78	-	23418.76	The QALY for S + SRS when compared to S + Cs-131 yield, making it significantly more cost-effective. SBRT for advanced hepatocellular carcinoma is cost-effective at a willingness to pay threshold as defined by WHO guideline in Taiwan. The ICER for gem-IMRT and gem-SBRT compared with gem-alone were \$2114574.59 and \$167300.10 per QALY gained, respectively. cost-effectiveness at threshold of \$157637.75 per QALY was 0% chance for gem-IMRT and 50% for gem-SBRT.
Leung et al (2016) [45]	S and stereotactic radiosurgery (SRS) [S + SRS] sorafenib	0.47	-	53736.40	
Leung et al (2016) [46]	Stereotactic body radiotherapy (SBRT) gemcitabine plus modern radiotherapy (Gem-IMRT)	3.07 2.81	- -	54958.17 33224.59	
	gemcitabine alone (Gem-alone) gemcitabine plus stereotactic body radiotherapy Gem-SBRT	- -	- -	- -	
Lester-Coll et al (2016) [47]	Stereotactic Body Radiation Therapy (SBRT) video-assisted thoracic surgery (VATS) wedge resection	0.85	-	568470.37	SBRT was cost effective for melanoma, with costs/net QALYs of 568470.37/0.85. In patients with NSCLC, the most cost-effective strategies were SBRT for AC (\$190457.45/0.80), paclitaxel/carboplatin for SCC (\$150444.68/0.48) and erlotinib for EGFRm AC (\$178749.89/1.90). Stereotactic body radiation therapy was marginally cost-effective for EGFRm AC compared to erlotinib with an incremental cost-effectiveness ratio of \$153487.62/QALY. For colon cancer, VATS wedge resection (\$179526.43/2.14) was the most cost-effective strategy.
	Systemic Therapy Stereotactic Body Radiation Therapy (SBRT)	0.87 0.80	- -	752828.57 190457.45	
	video-assisted thoracic surgery (VATS) wedge resection	0.78	-	199822.04	
	Paclitaxel/carboplatin /bevacizumab (PacCB)	0.68	-	225327.36	
	paclitaxel/carboplatin (PacC)	0.48	-	150444.68	In patients with 1 brain metastasis, the ICERs for SRS versus WBRT, SRS versus SRS+WBRT, and SRS+WBRT versus WBRT were \$142690.27, \$62399.80, and \$907775.68 per QALY gained, respectively. In patients with 2–10 brain metastases, the ICERs were similar: \$149784.80, \$71580.89, and \$997757.64 per QALY gained, respectively.
	Stereotactic Body Radiation Therapy (SBRT)	0.49	-	165988.73	
	video-assisted thoracic surgery (VATS) wedge resection	0.48	-	175130.93	
	Erlotinib Stereotactic Body Radiation Therapy (SBRT)	1.90 1.94	- -	178749.89 185273.26	
	Surgery video-assisted thoracic surgery (VATS) wedge resection	1.92 2.14	- -	197408.58 179517.92	In patients with 1 brain metastasis, the ICERs for SRS versus WBRT, SRS versus SRS+WBRT, and SRS+WBRT versus WBRT were \$142690.27, \$62399.80, and \$907775.68 per QALY gained, respectively. In patients with 2–10 brain metastases, the ICERs were similar: \$149784.80, \$71580.89, and \$997757.64 per QALY gained, respectively.
	Stereotactic Body Radiation Therapy (SBRT)	2.12	-	197782.88	
	fluorouracil plus oxaliplatin (FOLFOX)	1.60	-	205209.17	
	stereotactic radiosurgery (SRS)	0.94	-	41731.11	
Lester-Coll et al (2016) [48]	whole-brain radiation therapy (WBRT)	0.77	-	17623.31	In patients with 1 brain metastasis, the ICERs for SRS versus WBRT, SRS versus SRS+WBRT, and SRS+WBRT versus WBRT were \$142690.27, \$62399.80, and \$907775.68 per QALY gained, respectively. In patients with 2–10 brain metastases, the ICERs were similar: \$149784.80, \$71580.89, and \$997757.64 per QALY gained, respectively.
	SRS+WBRT stereotactic radiosurgery (SRS)	0.79 0.78	- -	32190.32 50424.89	
	whole-brain radiation therapy (WBRT)	0.63	-	26808.05	
	SRS+WBRT	0.64	-	26808.05	

(Continued)

Table 2. (Continued).

First author (Publication year)	Effectiveness			Main finding
	Treatment options	QALY	LY	
Kim et al (2016) [49]	Stereotactic Body Radiation Therapy (SBRT)	0.14	-	SBRT was found to not be a cost-effective treatment option compared with RFA using a WTP of \$122739.11/ QALY gained threshold. SABR is less costly than surgery. While lobectomy may be cost-effective compared to SABR, sublobar resection is less likely to be cost-effective. HA-WBRT and SRS plus HA-WBRT were cost-effective for 2 of the 4 cohorts, demonstrating the value of controlling late brain toxicity with this novel therapy. Cost-effectiveness depended on patient life expectancy. SRS was cost-effective in the cohorts with short prognoses (3 and 6 months), whereas HA-WBRT and SRS plus HA-WBRT were cost-effective in the cohorts with longer prognoses (12 and 24 months). SBRT is not a cost-effective strategy, resulting in an incremental cost-effectiveness ratio of \$152874.02 per QALY gained at a \$122739.11 per QALY gained willingness to-pay threshold. SBRT clearly contained more value than IMRT for external-beam treatment. Using a threshold of \$55360.76 per LYQ, SBRT seems cost effective.
Smith et al (2015) [50]	Radiofrequency Ablation	NA	-	
	stereotactic ablative radiotherapy (SABR)	3.6	-	
	sublobar radiation	4.1	-	
	lobectomy	4.7	-	
Savitz et al (2015) [51]	stereotactic radiosurgery (SRS)	1.68	-	Mean upfront costs for the 4,318 stage I cases were \$7964.77 for RT, \$9181.91 for SABR, \$12666.56 for sublobar resection, \$16942.11 for lobectomy, \$23893.96 for pneumonectomy, and \$15188.91 for BSC. SABR dominated (higher QALY, lower cost) RT, sublobar resection, and BSC. RT had lower initial costs than SABR that were offset by subsequent costs associated with recurrence. Lobectomy was cost effective when compared with SABR, with an ICER of \$58232.53.
	whole-brain radiotherapy [WBRT]	1.66	-	
	hippocampal avoidance WBRT [HA-WBRT]	1.80	-	
	SRS plus WBRT	1.73	-	
	SRS plus HA-WBRT	1.88	-	
Kim et al (2014) [52]	Stereotactic Body Radiation Therapy (SBRT)	0.53	-	SRS alone have similar overall survival and receive more cost-effective care than those treated with SRS+WBRT. Compared with SRS+WBRT, initial management with SRS alone does not result in a higher average cost.
	External Beam Radiation Therapy	0.47	-	
	Intensity-modulated radiation therapy (IMRT)	9.96	-	
Sher et al (2014) [53]	Nanorobotics SBRT	9.93	-	
	Robotic SBRT	9.93	-	
Mitera et al (2014) [54]	Stereotactic Body Radiotherapy (SBRT)	NA	3.86	SRS had a lower average cost per patient than SR, leading to an ICER of – 6005.56 per LY, meaning that using SRS costs 2702.50 less than SR per targeted patient, but increases LYs by 0.45 years. In patients who are MO, SBRT was the dominant strategy and thus the most cost-effective. For patients who are CO, lobectomy was the cost-effective treatment option (ICER \$16793.57/QALY). Compared with SRS and whole brain radiation therapy, SRS and observation not only had a higher average cost (\$101623.20 vs 163421.09 respectively) but also a higher average effectiveness (0.60 LYs vs 1.64 LYs, respectively) with an ICER of \$60741.83/LY or \$57380.03/QALY (with utilities captured using a 10-year horizon). Slightly higher ICER estimates were achieved with utilities captured using the other time horizons (\$59435.84/QALY and \$60512.49/QALY, respectively).
	Conventionally fractionated radiotherapy (CFRT)	NA	2.83	
Louie et al (2014) [55]	Stereotactic ablative radiotherapy (SABR)	-	-	
	Conventional radiotherapy	-	-	
	Best supportive care	-	-	
	Sublobar resection	-	-	The cost per life year gained was higher for SR than SRS (46.4 and 38.1 million VND, respectively).
	Lobectomy	-	-	
	Pneumonectomy	-	-	
Hall et al (2014) [56]	stereotactic radiosurgery (SRS) alone	-	9.8 month	
	SRS + whole-brain radiotherapy (WBRT)	-	7.4 month	
	surgery followed by SRS (S+SRS)	-	10.6 month	
Vuong et al (2013) [57]	Stereotactic radiosurgery (SRS)	-	1.53	Compared with SRS and observation not only had a higher average cost (\$101623.20 vs 163421.09 respectively) but also a higher average effectiveness (0.60 LYs vs 1.64 LYs, respectively) with an ICER of \$60741.83/LY or \$57380.03/QALY (with utilities captured using a 10-year horizon). Slightly higher ICER estimates were achieved with utilities captured using the other time horizons (\$59435.84/QALY and \$60512.49/QALY, respectively).
	surgical resection	-	1.08	
Shah et al (2013) [58]	SBRT in marginally operable	8.03	-	
	SBRT in clearly operable	8.21	-	
	wedge resection	7.93	-	
	lobectomy	8.89	-	The cost per life year gained was higher for SR than SRS (46.4 and 38.1 million VND, respectively).
Lincy et al (2012) [59]	SRS + Whole Brain Radiation Therapy (WBRT)	0.39	0.60	
	SRS + observation	1.48	1.64	
	SRS + Whole Brain Radiation Therapy (WBRT)	0.46	0.60	
	SRS + observation	1.52	1.64	
	SRS + Whole Brain Radiation Therapy (WBRT)	0.51	0.60	The cost per life year gained was higher for SR than SRS (46.4 and 38.1 million VND, respectively).
	SRS + observation	1.54	1.64	
	SRS + Whole Brain Radiation Therapy (WBRT)	-	-	
	SRS + observation	-	-	
	SRS + Whole Brain Radiation Therapy (WBRT)	-	-	

(Continued)

Table 2. (Continued).

First author (Publication year)	Treatment options	Effectiveness			Main finding
		QALY	LY	Cost*	
Puri et al (2012) [61]	stereotactic body radiation (SBRT) surgical intervention	-	2.94	18723.89	SBRT was estimated to have a mean expected survival of 2.94 years at a cost of \$18723.89 and surgical intervention was 3.39 years at a cost of \$23322.50, for an ICER of 10256.93. Based on the assumption that each treatment modality results in equivalent long-term efficacy, SBRT is a cost-effective strategy resulting in improved quality-adjusted survival compared to IMRT and PT for the treatment of localized prostate cancer. gem-SBRT had an ICER of \$93050.89 per QALY compared with gem-alone. gem-RT had an ICER of \$169767.67 per QALY compared with gem-alone. IMRT increased the ICER above \$1338861.72 per QALY compared with conventional RT. Gem-SBRT dominated the more costly and less effective options of gem-RT and gem-IMRT.
Parthan et al (2012) [62]	stereotactic body radiation therapy (SBRT) intensity-modulated radiation therapy (IMRT) proton beam therapy (PT)	- 8.11 8.05 8.17	3.39 - - -	23322.50 32526.59 45475.28 92457.85	
Murphy et al (2012) [63]	gemcitabine alone (gem-alone) gemcitabine plus conventional radiotherapy (gem-RT)	0.581 0.714	- -	57437.17 80197.82	
	gemcitabine plus intensity-modulated radiotherapy (gem-IMRT)	0.721	-	93050.89	
	gemcitabine with stereotactic body radiotherapy (gem-SBRT)	0.778	-	75913.46	
Hodges et al (2012) [64]	stereotactic body radiation therapy (SBRT) intensity-modulated radiation therapy (IMRT)	7.9 7.9	- -	29306.26 46873.88	SBRT dominated IMRT as a treatment strategy, and an ICER of < \$66148.12 per QALY was obtained in 66% of the model iterations. The incremental cost-effectiveness ratio for SBRT over 3D-CRT was \$8033.17/ QALY, and the incremental cost-effectiveness ratio for SBRT over RFA was \$18877.95/ QALY. In comparison to 3D-CRT and RFA, SBRT was the most cost-effective treatment. ICER of \$109.06 per QALY gained for carbon-ions compared to SBRT. Proton therapy and CRT were both less effective and more expensive, and thus dominated by both carbon-ion therapy and SBRT.
Sher et al (2011) [65]	three-dimensional conformal radiation therapy (3D-CRT) stereotactic body radiotherapy (SBRT) Radiofrequency ablation (RFA)	1.53 1.91 1.45	- - -	65392.68 68460.02 59777.50	
Grueters et al (2010) [66]	carbon-ions therapy protons therapy conventional radiotherapy (CRT)	2.67 2.33 1.98	- - -	31.16 44.70 36.80	
	stereotactic radiotherapy (SBRT)	2.59	-	22.35	
	carbon-ions stereotactic radiotherapy (SBRT)	3.16 3.20	- -	23.71 13.76	
Papatheofanis et al (2009) [67]	For operable stage I NSCLC CyberKnife stereotactic radiosurgery (SRS) external beam radiation therapy (EBRT)	0.28 0.20	- -	16661.09 19297.13	SBRT was on average more effective and less expensive than carbon-ion therapy. patients treated with CyberKnife SRS gained an additional net health benefit of 0.08 QALYs. CyberKnife SRS dominated the EBRT strategy and represented a cost-effective treatment option for this indication.

QALY: quality-adjusted life year; LY: life year gained. ICER: Incremental cost-effectiveness Ratio (2022 USD/QALY). *2022 USD. Not mentioned data was shown by -.

carbon ion therapy are cost-effective options than proton therapy and conventional radiotherapy [66].

3.2.3.2. Cost-effectiveness of proton-based technology in Prostate cancer. Comparing proton SRT with photon SRT for the treatment of localized prostate cancer showed that proton SRT is a cost-effective strategy [24]. In another study, it was shown that compared to IMRT and proton therapy, SRT is a cost-effective strategy that leads to improved quality-adjusted survival for the treatment of localized prostate cancer [62].

3.2.3.3. Cost-effectiveness of proton-based technology in Liver cancer. Proton therapy compared to linear accelerator radiosurgery technology is a cost-effective treatment for inoperable advanced hepatocellular carcinoma [41].

4. Discussion

Our comprehensive review of existing literature revealed that previous systematic reviews in this field focused only on specific types of cancer or particular SRT/SRS technologies [68–70]. Recognizing the limitations of these prior studies, our systematic survey aimed to provide a more comprehensive comparison of results across various types of cancer and a wide range of SRT/SRS technologies.

The findings of the present study showed that in most of these studies, SRT/SRS technologies are cost-effective strategies compared to competing options. Sensitivity analyses across various studies have consistently highlighted several factors crucial to the cost-effectiveness of SRT/SRS technologies. These include treatment effectiveness indicators such as tumor control, improvements in quality of life, reduction of side effects, and enhanced patient outcomes. Additionally, cost-related factors such as expenses associated with the stereotactic method itself (including equipment and procedural costs), hospitalization costs, follow-up expenses, and treatment of side effects significantly impact cost-effectiveness. Furthermore, long-term considerations, such as tumor recurrence rates, patient survival durations, and sustained improvements in quality of life, are pivotal in assessing the cost-effectiveness of these technologies. Other influential factors encompass patients' clinical statuses, advancements in technology and stereotactic techniques, as well as patient expectations.

Cost-effectiveness studies of SRT technology have only been conducted on some types of cancer so far. These cancers include lung cancer, prostate cancer, liver cancer, head and neck cancer, pancreatic cancer, kidney cancer, and some metastases.

Most of the studies have been related to lung cancer, and most of these studies have shown that SRT is cost-effective compared to its competing options. These competing options included CFRT, 3D-CRT, RFA, VATS, surgery, proton therapy, conventional radiotherapy, and in some cases lobectomy [26,32,37,50,54,55,61,65,66]. SRT technologies were not cost-effective compared to MWA, carbon ion radiotherapy, and in some cases lobectomy [21,22,35,50,55,58].

Regarding prostate cancer, SRT was cost-effective compared to all competing strategies. The competing options for treating this cancer were IMRT, fractionated IMRT, IMRT combined with

HDR-BT, monotherapy with high-dose-rate brachytherapy, LDR-BT, and proton therapy [31,43,53,62,64]. Only one study found that IMRT was both more effective and less costly than robotic SRT for localized prostate cancer treatment [39].

Concerning liver cancer, SRT was cost-effective compared to surgery, RFA, and sorafenib [30,45]. However, in some studies, it has been shown that SRT is not cost-effective compared to RFA and proton therapy [36,40,41,49].

With regard to head and neck cancer, SRT was identified as a cost-effective treatment compared to all competing options. The competing options included platinum-based chemotherapy alone, chemotherapy plus cetuximab, SRT plus cetuximab, and IMRT plus chemotherapy [29,38]. It was also shown that for renal cell carcinoma, SRT was economically superior to RFA as a competing option [25].

In the context of future research and publications on stereotactic therapeutics, several key issues should be considered for comprehensive cost-effectiveness analysis. These include the advancement of innovative technologies and methodologies, comparative assessments with alternative methods, formulation of treatment protocols, evaluation of long-term treatment outcomes, and adaptation to diverse clinical scenarios. Addressing these aspects as central themes in future publications can offer valuable guidance for enhancing the introduction of novel methods, improving treatment efficacy, and optimizing the allocation of financial resources within healthcare systems.

The adoption of stereotactic treatment modalities by countries and healthcare systems entails various consequences, such as the necessity to allocate increased financial resources, adjustments in reimbursement policies, and impacts on the sustainability of healthcare systems. These repercussions can directly influence access to healthcare services, insurance coverage, and the financial stability and performance of healthcare systems. A thorough assessment of these outcomes is imperative for making well-informed decisions regarding the integration of such therapies and for devising appropriate policies to manage their diverse effects effectively.

This review has several limitations. Due to the databases used and the selection of specific words, some studies may have been omitted. Additionally, due to language constraints, only English language articles were reviewed in this study. Another limitation was the lack of access to the full text of a few articles, but this was resolved through correspondence with the authors.

5. Conclusion

Overall, the findings of various studies suggest that SRT/SRS technology is a cost-effective strategy in most cases for treating cancers compared to alternative treatments. Therefore, the use of this technology is recommended for optimal resource consumption.

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REVIEW



Focal therapy for oligometastatic and oligoprogressive renal cell carcinoma: a narrative review

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ABSTRACT

Metastatic renal cell carcinoma (RCC) can present with oligometastatic disease and/or develop oligoprogression following systemic therapy. Cytorreductive and focal metastasis-directed therapy options include resection, stereotactic ablative radiation and thermal ablation. Aggressive focal therapy may allow delay in initiation of or modification to systemic therapy and improve clinical outcomes. In this narrative review we synthesize current practice guidelines and prospective data on focal therapy management options and highlight future research. Patient selection and the choice of focal treatment techniques are controversial due to limited and heterogeneous data and patients may benefit from multidisciplinary evaluation. Prospective comparative trials with clearly defined inclusion criteria and relevant end points are needed to clarify the risks and benefits of different approaches.

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1. Introduction

The annual global incidence of kidney cancer is approximately 430,000 cases [1]. Ninety percent are renal cell carcinomas (RCC), of which approximately 70% have clear cell histology [2]. While the overall incidence of RCC has risen over the last decades, driven by increased detection of incidental renal masses, the rates of metastatic disease and mortality have not declined significantly [2,3]. Approximately 13% of patients present with metastatic disease, most commonly involving the lung, followed by bone, liver and brain; among patients in the US Surveillance, Epidemiology and End Results (SEER) population-based cancer registry with only a single organ site of distant disease, the relative frequencies were 25% lung, 17% bone, 5% liver and 2% brain [4,5].

Metastatic RCC has historically been considered incurable, with systemic treatments aimed at prolonging Progression-Free Survival (PFS) and focal treatments reserved for palliation to maintain quality of life. Surgical resection, stereotactic ablative radiotherapy (SABR) that precisely delivers high-dose radiation and thermal ablation have been used to cytorreduce the primary site and control metastatic foci. Patients who present with low-volume metastatic disease or demonstrate disease progression at a limited number of sites after systemic therapy are defined as having oligometastatic or oligoprogressive disease, respectively [6,7]. The first evidence of benefits from treatment of metastases in the oligometastatic setting was the Phase II randomized trial SABR-COMET, which showed that Metastasis-Directed Therapy (MDT) with SABR extended Overall Survival (OS) compared with standard systemic therapy alone in a

population that included RCC [8]. The survival benefits from this approach are supported by Phase II trials for other histologies [9–11].

Modern systemic therapy (including vascular endothelial growth factor receptor-tyrosine kinase inhibitors [VEGFR-TKIs], and/or immune checkpoint inhibitors [ICIs]) for RCC has improved OS for patients with metastatic disease, which offers additional opportunities for focal interventions. Yet these systemic therapies also come with common high-grade toxicities (40–60% with doublet ICI [12] and above 70% in recent ICI/VEGFR-TKI combination trials [13,14]). Furthermore, VEGFR-TKI therapies are typically given in an ongoing, indefinite fashion resulting in chronic symptoms which can adversely impact quality of life [15]. Effective treatment of oligometastatic or oligoprogressive disease may allow delay to initiation of systemic treatment or a treatment-free interval. The aim of this narrative review is to synthesize prospective data and clinical practice guidelines on cytoreductive and metastasis-directed therapy for oligometastatic and oligoprogressive RCC that inform current management strategies, and highlight areas of future research.

2. Methods

PubMed was queried using the search terms ((renal cell OR kidney) AND (carcinoma OR cancer)) AND metast* for English language results through 12/31/2023, and guidelines were reviewed (Table 1). Additional sources were identified from bibliographies. Active or recruiting trials were identified on clinicaltrials.gov. Bone-modifying agents, radiopharmaceuticals, palliative treatments and systemic therapy were beyond the scope of this review. Data and recommendations were limited to non-hereditary RCC with clear cell histology, reflecting its epidemiologic predominance. All Confidence Intervals (CI) described are 95% and data were rounded to the nearest whole number.

3. Definition of oligometastatic & oligoprogressive disease

In this review, **oligo-states** were defined in line with the ESTRO-EORTC classification system as ≤ 5 **extracranial foci** [7]. **Oligometastatic** disease can be **synchronous** within 6 months of diagnosis (also called *de novo* oligometastatic) or **metachronous** ≥ 6 months after initial diagnosis of locoregional disease (also known as oligorecurrence), while **oligoprogressive** disease involves progression after systemic therapy.

4. Evaluation prior to cytoreductive or Metastasis-Directed Therapy

Imaging should include contrast-enhanced CT of the chest, abdomen and pelvis. Nuclear medicine bone scan is recommended by practice guidelines for evaluation of bone pain or elevated serum alkaline phosphatase, but notably lacks sensitivity for the osteolytic lesions that are characteristic of RCC [34], which limits its use for screening asymptomatic patients. Abdominal MRI with contrast may improve assessment of locoregional disease extent, which may influence the feasibility of resection and ablative treatments for patients with synchronous metastases. The EAU and Society for Immunotherapy of Cancer guidelines recommend baseline CNS imaging for all patients with metastatic disease [21,31], and the American Society of Clinical Oncology highlights its necessity prior to active surveillance [16] but other guidelines only recommend consideration of baseline CNS imaging or as clinically indicated, with contrast-enhanced MRI the preferred modality. Baseline CNS imaging with MRI is reasonable, as retrospective data suggests that 8–15% of patients have brain metastases at the time of metastatic diagnosis [27]. An International Kidney Cancer Coalition (IKCC) expert panel reported that 58% recommended routine baseline brain MRI upon diagnosis of metastatic disease [27]. No guidelines endorse the use of PET imaging, and renal excretion makes evaluation of primary tumors difficult. Novel PET tracers may improve the detection of metastatic disease [35,36], which is an important prerequisite to correctly classify oligometastatic states [7].

No guidelines recommend routine molecular or somatic genetic testing for non-hereditary RCC in patients who present with metastatic disease. Although mutations in the *BAP-1* tumor suppressor gene have been associated with synchronous metastatic disease and poor prognosis [37,38], foci of disease demonstrate a high degree of intratumoral heterogeneity [39] and primary and metastatic sites demonstrate a high degree of mutational discordance, limiting the utility of tissue analysis from any single site of disease [40].

4.1. Clinical risk groups

All clinical guidelines stratify patients per the International Metastatic RCC Database Consortium (IMDC) prognostic risk groups, based on factors associated with survival in the VEGFR-TKI era [41]. Median OS ranges from 9 months (2-year OS of 7%) for poor risk disease, and median OS of 27 months (2-year OS of 53%) for intermediate disease, to median OS unreached (2-year OS of 75%) for favorable risk disease, demonstrating the heterogeneity of natural histories and treatment responses that are associated with these risk factors, which include perfor-

Table 1. Professional society guidelines reviewed.

Professional society	Scope	First author	Year	Ref.
American Society of Clinical Oncology (ASCO)	Management of metastatic RCC	Rathmell	2022	[16]
American Urological Association (AUA)	Management of localized RCC	Campbell	2021	[17]
Cardiovascular and Interventional Radiological Society of Europe (CIRSE)	Thermal ablation of lung metastases	Venturini	2020	[18]
European Association of Urology (EAU)	Thermal ablation of bone metastases	Ryan	2022	[19]
	Cytoreductive nephrectomy	Bex	2018	[20]
	Management of RCC	Ljungberg	2022	[21]
	Adjuvant immune checkpoint inhibitor therapy	Bedke	2023	[22]
European Society of Clinical Oncology (ESMO)	Management of RCC	Escudier, Powles	2019, 2021	[23,24]
National Comprehensive Cancer Network (NCCN)	Management of RCC	NCCN guidelines panel	2023	[25]
Pan-Asian Adapted ESMO Guidelines (PAGA)	Management of RCC	Kanesvaran	2021	[26]
International Kidney Cancer Coalition (IKCC)	Management of brain metastases from RCC	Hasanov	2022	[27]
International Kidney Cancer Coalition (IKCC)/German Cancer Society renal working group	Management of bone metastases from RCC	Grünwald	2018	[28]
Kidney Cancer Research Network of Canada (KCNC)	Management of advanced RCC	Canil	2021	[29]
Latin American Cooperative Oncology Group/Latin American Renal Cancer Group (LACOG/LARCG)	Management of metastatic RCC	Soares	2020	[30]
Society for Immunotherapy of Cancer (SITC)	Management of advanced RCC	Rini	2019	[31]
Society of Interventional Radiology (SIR)	Percutaneous ablation of metastases from RCC	Morris	2020	[32]
	Percutaneous ablation of lung metastases	Genshaft	2021	[33]

RCC: Renal cell carcinoma.

mance status, start of systemic therapy within 1 year of diagnosis and metabolic changes. These risk groups have been externally validated for patients treated with first-line VEGFR-TKI monotherapy and second-line targeted therapy [42]; a heterogeneous cohort with short follow-up suggests that IMDC groups estimate prognosis consistently across first-through fourth-line treatment with various combinations of immunotherapies and VEGFR-TKIs as well [43].

The IMDC risk groups do not account for the anatomic distribution, volume, or velocity of metastases and refined prognostic and predictive tools are needed to select patients for focal treatment of metastases. Analysis of the first site of metastasis suggested that brain, bone, and/or liver metastases move 15% of patients into a higher-risk group, many of whom received MDT to this site, but the influence of MDT on outcomes was not evaluated [44]. A similar study found that bone metastases were independently associated with worse OS, but did not evaluate the number and location of bone metastases or the use of focal therapy [45]. Franzese et al. developed prognostic risk groups based on 129 patients with mostly metachronous metastatic disease who received stereotactic radiotherapy to oligometastatic or oligoprogressive foci [46]. The strongest multivariable predictor of OS was the presence of brain metastases (Hazard Ratio [HR] 4.5, CI: 2.2–9.2). Recursive partitioning analysis found that age and treatment of intracranial or bone disease stratified 3-year OS from 10% (any age treated for intracranial

disease) to 83% (age ≤ 65 years treated for non-osseous extracranial disease). In the future, risk groups developed for pan-cancer metastatic disease that account for the location and history of metastases may improve patient selection for metastasis-directed therapy. For example, the ESTRO-EORTC oligo-disease classification system has been prospectively validated to predict PFS and OS in a multi-center cohort treated with ablative radiation [47], and data on the subset with RCC in the ongoing OligoCare prospective registry study (NCT03818503) may improve patient selection in the future. Alternative prognostic groups for metastatic disease have been developed [48], but not yet prospectively evaluated or adopted by guidelines.

5. Focal therapy for oligometastatic & oligoprogressive RCC

Systemic management options for metastatic disease include the use of best supportive care, active surveillance (AS), which defers systemic therapy to delay treatment resistance and maintain quality of life by avoiding potential systemic therapy toxicity, or initiation of systemic therapy. Focal treatment may be indicated for palliation at any point in the disease trajectory.

For patients with synchronous metastases, focal therapy may include cytoreduction of the primary as well as treatment of distant metastases. Upfront treatment to all sites of disease may enable the safe deferment of systemic

therapy, improve quality of life and potentially provide curative avoidance of systemic therapy altogether if no new sites of progression develop. In 1939, the first report of focal treatment to all oligometastatic foci for any histology involved a patient with RCC with a single synchronous lung metastasis who lived at least 5 years after nephrectomy followed by lung irradiation without subsequent systemic therapy [49].

In oligoprogressive scenarios, the goal of focal therapy is to control foci whose resistance to systemic therapy threatens discontinuation of otherwise efficacious and well-tolerated systemic agents and allow for possible holidays from systemic agents with bothersome toxicities [15,50]. Oligoprogressive disease is a complex, heterogeneous clinical category that includes patients who may have initially presented with synchronous or metachronous, mono- or polymetastatic disease and already received systemic therapy, focal therapy, or multimodality treatment. As such, it includes a spectrum of biological aggressiveness and resistance to systemic therapies, as detailed in the ESTRO-EORTC classification schemes [7] and presents unique management challenges.

Contemporary focal treatment options include surgery (historically the most commonly applied approach), stereotactic ablative radiotherapy, or thermal ablation. In the past, RCC was considered resistant to conventional radiation techniques and radiation therapy was often reserved for palliation. However, the development of SABR (also known as stereotactic body radiotherapy, SBRT), which delivers escalated tumor doses while minimizing radiation exposure of normal tissues through precise image guidance [51–53], has shifted the paradigm as the higher doses overcome radioresistance [54,55]. Percutaneous thermal ablation techniques (most commonly radiofrequency ablation, cryoablation, or microwave ablation) [32] have also been used, with most reports pre-dating the development of SABR. No prospective comparisons with oncologic outcomes have been made between focal treatment techniques. Clinical guidelines on the management of metastatic RCC reflect regional practice patterns and resources in Europe [21,23,24], the Americas [16,17,25,29,30] and Asia [26], as well as consensus from international societies [28,31]. A flow chart of potential patient selection criteria for focal therapy is presented in Figure 1. All patients should be discussed in a multidisciplinary setting and enrolled in a clinical trial when possible.

5.1. Focal therapy & active surveillance

All prospective active surveillance studies allowed focal therapy prior to or during AS, but the role

of focal therapies in enabling patients to start or continue AS, as well as the safety of avoiding focal therapy during AS, both require prospective investigation.

The prospective trial by Rini et al. evaluated time to start of systemic therapy in 48 patients with good performance status and metachronous metastatic disease after nephrectomy [56]. Most (75%) had 1–2 IMDC risk factors; 83% had involvement of 1–2 organs but the number of specific metastases was not reported. With median follow-up of 38 months, median duration of AS was 15 (CI: 11–25) months and 65% started systemic therapy for disease progression. Only 26% developed new sites of disease. Seven patients (15% overall) received MDT as consolidative, curative-intent therapy after radiographic, asymptomatic progression of a single site during AS. Two patients developed symptomatic intracranial progression, with one patient dying from CNS disease prior to starting systemic therapy. Notably, patients were screened with head CT rather than brain MRI at baseline, so the prevalence of CNS metastases may have been under-appreciated. Harrison et al. reported on 143 patients who had ≥ 3 months of AS, with a median duration of 33 (CI: 29–34) months prior to systemic therapy [57]. Median OS was unreached for the third of patients without measurable disease at the start of AS, but the use of MDT prior to AS was not reported. Kushnir et al. evaluated 853 patients who received ≥ 6 months of AS, with a median duration 14 (CI: 6–71) months, compared with 827 patients who started systemic therapy sooner [58]. Approximately half of each cohort had a cytoreductive nephrectomy, and the AS cohort had higher rates of surgical metastatectomy (37 vs. 14%) at unknown time points.

Patient selection for focal therapy prior to or during AS should be investigated further. Rini et al. found that ≤ 2 metastatic sites was associated with prolonged AS on multivariable analysis. However, two different retrospective cohorts did not confirm this association, perhaps due to few patients with > 2 metastatic sites and/or the high frequency of focal therapy use during AS, and instead suggested that physiologic and radiographic tumor burden were associated with prolonged AS and prolonged overall survival, respectively [59,60]. All guidelines agree that AS is not the preferred management strategy for any group of patients, but that AS may be considered for patients with oligometastatic disease, between 0 and 2 IMDC risk factors, favorable disease kinetics, low symptom burden, and/or significant comorbidities. In the Rini trial CT body imaging was repeated at 3-month intervals (year 1), 4-month intervals (year 2), then 6-month intervals during AS, until systemic therapy started per physician and patient decision, and this schedule has been adopted by

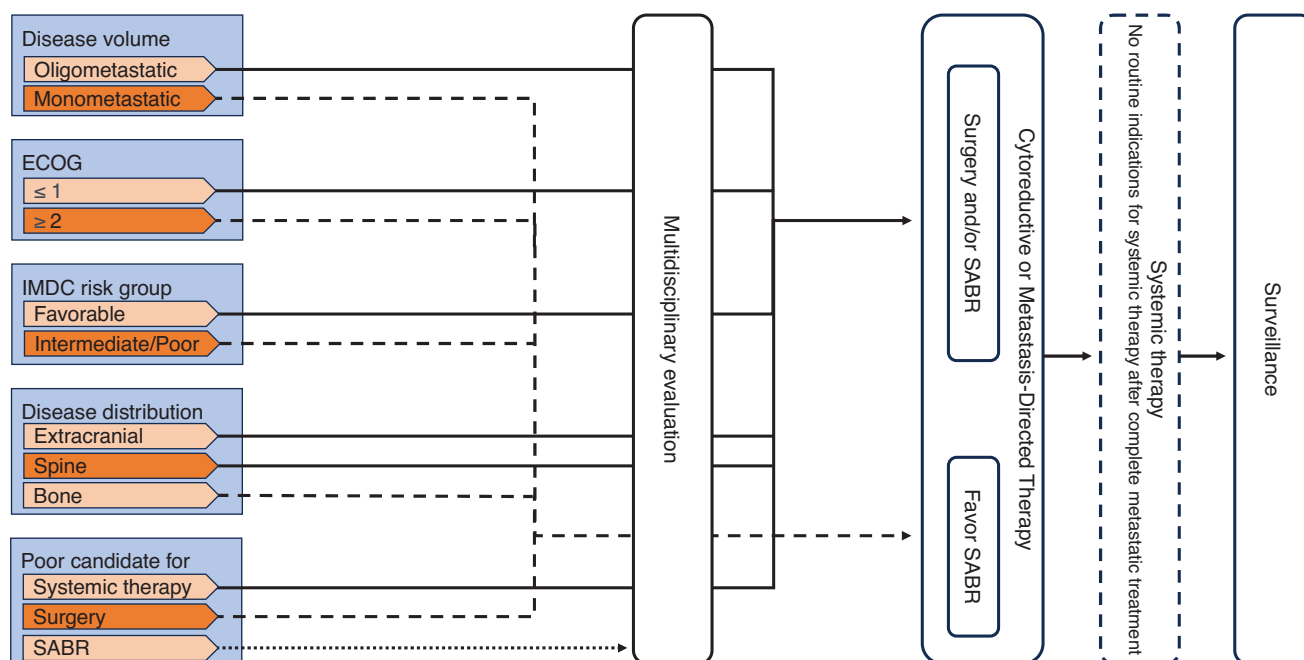


Figure 1. Potential selection factors for focal therapy (— Surgery/SABR; --- SABR; ... Multidisciplinary discussion).

other institutions [59,60]. Although CNS imaging was not initially protocolized, annual CNS surveillance began after intracranial progression was noted during the study.

6. Cyto-reductive therapy

6.1. Nephrectomy

In the era of interferon (IFN) therapy, the standard of care for patients with synchronous metastatic disease involved cyto-reductive nephrectomy (CN) followed by IFN because of OS benefits compared with IFN alone, based on the results of SWOG 8949 and EORTC 30947 [61]. After VEGFR-TKI therapy demonstrated superiority to IFN, the unclear additive benefit of CN and the risk of surgical selection bias prompted two trials (CARMENA and SURTIME) that prospectively examined the benefits and timing of CN in surgically-fit patients with technically resectable primary disease and synchronous intermediate- or poor-risk disease metastatic disease based on the historical MSKCC risk grouping [62].

CARMENA demonstrated that OS with sunitinib alone was non-inferior to CN followed by sunitinib (HR: 0.89, CI: 0.71–1.10) based on the intention-to-treat analysis [63]. Although the majority had excellent performance status and intermediate-risk disease, >40% in each arm had poor-risk disease, and >20% in each arm did not receive their allocated intervention. An exploratory analysis found that better performance status and favorable risk grouping was associated with survival benefits from upfront cyto-reduction. SURTIME attempted to address

the question of surgical timing by comparing PFS in patients with CN before versus after sunitinib, but the under-powered results showed no difference [64]. Patients were more likely to receive sunitinib in the deferred CN arm (98% versus 80% in the upfront CN arm), and 29% avoided CN due to early disease progression, which suggests that upfront CN may delay systemic therapy and provide minimal if any benefit for unselected patients whose disease trajectory is unclear. Exploratory analysis suggested that deferred CN was associated with prolonged OS, although at the cost of increased morbidity, as overall half of the patients who received CN developed surgical complications, including 3 deaths (3%). Post-hoc analysis found that upfront CN was associated with delayed initiation and shorter duration of systemic therapy as well as decreased radiographic response, suggesting that patients with intermediate- and poor-risk disease may benefit from upfront systemic therapy [65]. The results of both trials may not be generalizable to patients with frailty or comorbidities, regardless of IMDC risk group. Ongoing Phase II and III studies of CN and immunotherapy include NORDIC-SUN (NCT03977571), Cyto-KIK (NCT04322955), PrimerX (NCT05941169) and PROBE/SWOG 1931 (NCT04510597) (Table 2).

6.2. Stereotactic ablative radiotherapy

Correa et al. evaluated 372 patients from small retrospective and prospective studies in a meta-analysis of local control (LC) and toxicity after SABR for localized

Table 2. Ongoing studies of cytoreductive and metastasis-directed therapy for renal cell carcinoma.

Study	IMDC risk group	Cytoreductive nephrectomy		Cytoreductive or focal SABR recommended	Ref.
		Recommended	Not recommended		
ESMO	Intermediate/poor	Palliation or consolidation	Asymptomatic primary disease	Emerging role in oligo-disease states	[23,24]
	Favorable/intermediate	Oligometastatic, good PS, AS candidates			
EAU	Favorable/intermediate	Oligometastatic and good PS	Patients receiving upfront ICI	ND	[20,21]
	Any	May consider for consolidation after 3 months of VEGFR-TKI			
PAGA	Any	Oligometastatic, good PS, or palliation; either up-front or consolidative	Unclear benefit for patients with synchronous metastatic disease who receive TT/IO	Only for palliation of symptomatic primary disease	[26]
NCCN	Any	May consider for good PS and no CNS disease or palliation, oligometastatic disease eligible for complete metastasectomy		ND	[25]
ASCO	Favorable/intermediate (1 risk factor)	Should be considered for good PS, no bone, liver, or brain disease, low extrarenal tumor burden	High extrarenal disease burden	ND	[16]
	Poor	May consider for consolidation after ST			
	Any	Palliation			
AUA		Oligometastatic disease		Oligometastatic disease	[17]
KCRCN	Any	Oligometastatic, good PS, minimal symptoms, resectable disease	High systemic symptom burden, active CNS disease, high extrarenal disease burden, rapid progression, poor PS, limited prognosis	Consider for complete metastasectomy only	[29]
		May consider for consolidation after ST if significant and stable response			
LACOG/LARCG	Favorable/intermediate	May consider for oligometastatic and good PS, or AS candidates, especially if candidate for total metastasectomy	Poor risk, symptomatic metastases, presence of brain, bone, liver and/or multi-visceral disease	ND	[66]
	Any	Palliation; may consider for consolidation			
SITC	Favorable	Low extrarenal tumor burden	Poor risk, brain disease, high extrarenal disease burden	ND	[31]

ASCO: American Society of Clinical Oncology; AUA: American Urological Association; AS: Active surveillance; CNS: Central nervous system; EAU: European Association of Urology; ESMO: European Society of Clinical Oncology; ICI: Immune checkpoint inhibitor; KCNC: Kidney Cancer Research Network of Canada; LACOG/LARCG: Latin American Cooperative Oncology Group/Latin American Renal Cancer Group; NCCN: National Comprehensive Cancer Network; ND: Not discussed; PAGA: Pan-Asian Adapted ESMO Guidelines; PS: Performance status; SITC: Society for Immunotherapy of Cancer; ST: Systemic therapy; VEGFR-TKI: Vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

RCC [68]. Almost all (91%) were ineligible for cytoreductive surgery, and 20% had stage 3–4 disease. LC was 97% (CI: 94–100%) while grade 3–4 toxicity was 1.5% (CI: 0–4%). Longer 5-year LC data comes from a patient-level meta-analysis of retrospective and prospective observational data from the multi-center International Radiosurgery Oncology Consortium for Kidney (IROCK) cohort of 190 patients (75% inoperable), which estimated 94% LC (CI: 90–97%); only 1 patient experienced grade 3+ toxicity [69]. Although not all patients in these cohorts had metastatic disease, the high proportion of surgically-ineligible patients supports generalizing to the metastatic setting. These data suggest that SABR provides excellent local control with minimal high-grade toxicity. A recent meta-analysis of randomized trials of cytoreductive surgery or radiation for diverse primary

histologies found that for patients with low metastatic burden, cytoreductive radiation was associated with improved OS (HR: 0.67, CI: 0.52–0.85) [70], and ongoing studies are investigating the role of cytoreductive SABR for RCC in combination with immunotherapy, including CYTOSHRINK (NCT04090710) and SAMURAI/NRG-GU012 (NCT05327686) (Table 2).

6.3. Thermal ablation

There are no prospective data on thermal ablation for primary disease in the metastatic setting. Multiple guidelines on the management of localized RCC limit its use to lesions <3–4 cm, with the caveat that multiple treatments may be needed to achieve LC rates equivalent to surgical resection [17,21,23,25]. It is unclear how

generalizable these recommendations are for patients with metastatic disease. *Trans*-arterial radioembolization with Yttrium-90 [71] or chemoembolization [72] are novel treatments for primary disease that did not show major toxicity in small Phase I studies and may expand the armamentarium in the future, but current trials focus on the use of RFA or thermal ablation (Table 2).

6.4. Patient selection for cytoreductive therapies

CN may offer survival benefits for a subset of patients [73], and prognostic models have been developed to improve patient selection [74,75]. Upfront CN risks include over-treatment with focal surgery in patients with aggressive disease who experience rapid distant progression, develop surgical complications that preclude or delay systemic therapy, or do not tolerate systemic therapy due to toxicity. On the other hand, upfront systematic therapy offers prognostic information regarding the tempo and trajectory of disease and response to therapy, sparing patients with early polyprogression from surgical morbidity and potential delays to systemic therapy. CN is essential for palliating obstruction, bleeding, pain, or metabolic derangements, but given the absence of randomized evidence, and the inherent surgical selection bias with observational data, patients may benefit from multidisciplinary discussion, with surgery performed at high-volume centers when feasible due to the complexity and perioperative risks of this operation [76]. Guidelines typically recommend consideration of upfront CN for patients with lower IMDC risk groups, lower burden of disease, better performance status and low symptom burden, while recommending upfront systemic therapy for patients with higher risk groups, worse performance status, and/or more extensive or symptomatic extrarenal disease (Table 3).

Prospective comparative trials are needed to clarify the relative benefits of CN versus SABR and patient selection criteria. The non-invasive nature of SABR expands the eligible pool of patients to whom cytoreductive treatment may be offered, and the low risk of complications without need for post-intervention healing or rehabilitation minimizes delays and interruptions to systemic therapy. Although ESMO notes an emerging role for SABR [23], few guidelines recommend it as an alternative to CN (Table 3). The EAU does not discuss SABR for localized disease [21], while the American Urological Association (AUA) considers it investigational in this setting [77]. Pending updated guidelines, multidisciplinary discussion of SABR is recommended for patients who are not surgical candidates. No guidelines recommend thermal ablation.

7. Metastasis-directed therapy

7.1. Metastatectomy

Surgical resection of all metastatic RCC foci (total surgical metastatectomy) has long been utilized to render patients disease-free, and recent meta-analyses of observational studies have found associations with prolonged OS, PFS and Freedom from Systemic Therapy (FFST) [78–81]. Operability and resectability may be precluded by medical comorbidities, the risk of interrupting or delaying systemic therapy and the expected morbidity of surgery. Real-world experience suggests about 50% experience complications after metastatectomy, with approximately 25% overall requiring subsequent procedural interventions [82,83], while retrospective data from two high-volume centers found a 30-day overall complication risk of 26% [84]. Complication risks may reflect the location and number of resections and unmeasured confounders such as comorbidities, expertise and supportive care [82–85].

7.2. Stereotactic ablative radiotherapy

Multiple studies support the efficacy and safety of SABR for ablation of extrarenal metastases, particularly for CNS and bone disease, where radiation is often considered standard of care. For extracranial disease, meta-analysis of studies from 2005–2018, mostly retrospective, estimates 89% (CI: 84–95%) 1-year LC and 1% (CI: 0–2%) grade 3+ toxicity [86,87]. Although SABR offers effective short-term LC without the risks, complications, or interruptions to systemic therapy often associated with surgery, longer follow-up is needed to clarify LC durability and confirm benefits for survival and quality of life.

Two small prospective trials of sequential total metastatic ablation with SABR have been conducted. Tang and colleagues showed excellent LC and safety in 30 patients with metachronous RCC treated with SABR or hypofractionated dose-escalated radiotherapy [88]. Almost half (47%) had IMDC favorable-risk disease and 67% had only one anatomic site of disease at enrollment (median number of metastases 1, range 1–4). A minority (30%) had prior systemic therapy with a single line of therapy, with toxicity being the most common reason for cessation, while 40% had prior focal therapy with either surgery, definitive radiation, or cryotherapy. All metastatic sites were treated and 43% received a second course during the study period (77% to a single site of progression). With median follow-up of 18 months (IQR 13–27), 1-year LC was 97%. Median PFS was 23 (CI: 11-unreached [UR]) months, 1-year PFS was 64% (CI: 48%–85%), median systemic-therapy-free survival was UR (CI: 16 months-UR) and 1-year FFST) was 82% (CI: 70%–

Table 3. Guideline considerations for cytoreductive and metastasis-directed therapy with surgery or stereotactic ablative radiation.

Topic	Country	NCT, name	Design	Population (N)	Intervention	Primary outcome	Study end (year)	Ref.
Oligometastatic disease								
	Europe	NCT03818503, OligoCare	Registry	Metastatic disease (2000)	N/A	Use of radiation	2024	
Cytoreductive therapy								
	Australia/Canada	NCT04090710, CYTOSHRINK	Phase II	Synchronous unresectable IMDC intermediate/poor risk RCC (78)	SABR with ICI/ICI	PFS	2024	
	Denmark	NCT03977571, NORDIC-SUN	Phase III	Synchronous IMDC intermediate/poor risk RCC (400)	Delayed CN after ICI/ICI or ICI/VEGFR-TKI	OS	2026	
	USA	NCT04322955, Cyto-KIK	Phase II	Synchronous metastatic RCC (48)	Delayed CN after ICI/VEGFR-TKI	CR	2027	
	Netherlands	NCT05941169, PrimerX	Phase III	Synchronous metastatic RCC (750)	Delayed CN after ICI/ICI or ICI/VEGFR-TKI	OS	2031	
	USA	NCT05327686, SAMURAI/NRG-GU012	Phase II	Unresectable locally-advanced or IMDC intermediate/poor risk RCC (240)	SABR with adjuvant ICI/ICI or ICI/VEGFR-TKI	OS and PFS	2032	
	USA	NCT04510597, PROBE/SWOG 1931	Phase III	Synchronous metastatic RCC (364)	Delayed CN after ICI or ICI/VEGFR-TKI	OS	2033	
Metastasis-directed therapy								
	USA	NCT03696277	Phase II	Oligoprogressive RCC (20)	SABR	FFST	2024	
	USA	NCT02956798	Phase II	Oligometastatic RCC (23)	SABR	FFST	2024	
	USA	NCT03599765, EXTEND	Phase II	Oligometastatic mixed histology including RCC (367)	Surgery or thermal ablation prior to systemic therapy	PFS	2025	
	France	NCT04299646, GETUG-StORM-01	Phase II	Oligoprogressive RCC after systemic therapy (114)	SABR	PFS	2026	
	USA	NCT04974671	Phase II	Oligoprogressive RCC after ICI (30)	SABR with any other MDT	PFS	2027	
	Canada/Ireland/UK/USA	NCT03862911, SABR-COMET-3	Phase III	Oligometastatic mixed histology including RCC (330)	SABR with systemic therapy	OS	2028	
	Canada/UK/Australia/Netherlands	NCT03721341, SABR-COMET- 10	Phase III	Polymetastatic mixed histology including RCC (204)	SABR with systemic therapy	OS	2029	
	Europe	NCT04498767, OligoRARE	Phase III	Oligometastatic mixed histology including RCC (200)	SABR with systemic therapy	OS	2030	
Immune response and safety								
	USA	NCT03065179, RADVAX	Phase II	Metastatic RCC (29)	SABR with ICI/ICI	Safety and ORR	2020	[67]
	Italy	NCT01884961, IL2HD	Phase II	Mixed histology including RCC (35)	SABR with high dose IL-2	Immune biomarkers	2022	
	USA	NCT02542202	Phase I	Oligometastatic/locally recurrent RCC (25)	SABR	Safety	2023	
	Australia	NCT05024318, NAPSTER	Phase II	Synchronous metastatic RCC (26)	SABR with ICI prior to CN	Immune and pathologic response	2023	
	USA	NCT05112627	Phase I	Metastatic RCC (45)	SABR or RFA	Immune biomarkers	2024	
	USA	NCT05830058	Phase I	Oligoprogressive mixed histology including RCC (32)	PET-adapted SABR	Safety and feasibility	2026	
	France	NCT05259319, IMMUNOs-SBRT	Phase I	Metastatic mixed histology including RCC (92)	SABR with ICI/tiragolumab	Safety	2030	

CN: Cytoreductive nephrectomy; CR: Complete response; FFST: Freedom from systemic therapy; ICI: Immune checkpoint inhibitor; IL: Interleukin; IMDC: International Metastatic RCC Database Consortium; N: Target enrollment; ORR: Objective response rate; OS: Overall survival; PET: Positron-emission tomography; PFS: Progression-free survival; RCC: Renal cell carcinoma; RFA: Radiofrequency ablation; SABR: Stereotactic ablative radiation; VEGFR-TKI: Vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

98%). The most common reason for starting systemic therapy (20%) was radiographic progression that was not amenable to SABR. Three patients (10%) had grade 3+ toxicity from SABR: 2 with self-resolving neuromuscular symptoms and 1 with grade 4 hyperglycemia. Follow-up is ongoing for a second cohort that aims to evaluate the feasibility of sequential SABR in patients with low-volume metastatic disease with the primary outcome of 1-year PFS (NCT03575611).

A more recent study by Hannan et al. evaluated the feasibility of upfront SABR to delay systemic therapy [89]. Twenty-three patients were enrolled, 74% with favorable-risk disease, almost all of whom had metachronous metastases, and 30% of whom had prior MDT with surgery or radiation. Sixty-five percent had only a single site of disease at enrollment; 10 (43%) received a second course of SABR during the study. At median 22 months (IQR 16–30) follow-up, LC was 100%. One-year FFST was 91% (CI: 70%–98%), median time to systemic therapy was UR, 1-year PFS was 83% (CI: 60–93%), and median PFS not yet reached. There were no clinically significant quality of life changes overall, but there was one potential grade 5 toxicity (a patient who died from septic shock due to immune colitis within 3 months of SABR). This small study demonstrated that SABR may provide durable delay of systemic therapy.

Specifically for oligoprogressive disease, Cheung et al. conducted a single-arm prospective multisite Phase II trial of SABR for oligoprogression after VEGFR-TKI monotherapy [90]. The study was closed early due to the slow accrual of 37 patients (32% IMDC favorable risk, 46% with synchronous metastases, 54% with a single site of progression after median 19 months of VEGFR-TKI therapy, almost all using sunitinib as first-line therapy). Three of the lesions treated were intracranial. Although the primary end point of LC was 93% (without any grade 3+ toxicities), after median 1 year follow-up the 1-year PFS was only 43% due to progression at new sites, with median PFS of 9 (CI: 8–16) months. About one-fifth received additional courses of radiation prior to changing systemic therapy, and overall, 73% changed systemic therapy during follow-up. *Post hoc* analysis estimated the 1-year cumulative incidence of changing systemic therapy was 47% (CI: 32–68%), with median time to change of 13 (10–17) months. Exploratory analysis of PFS predictors suggested that longer durations of disease control from systemic therapy prior to SABR was associated with longer PFS after SABR. Advances in systemic therapy during the study period limited the number of eligible patients, and as all patients received VEGFR-TKI monotherapy, it is unclear how applicable these results are to modern

treatment paradigms where ICI or combination therapy is an option for many patients.

In a single-arm Phase II study, Hannan et al. demonstrated that sequential SABR to oligoprogressive foci enabled continuation of systemic therapy without adversely affecting quality of life [91]. Of 20 patients, 25% had IMDC favorable-risk disease, 60% had synchronous metastases, only 20% were on first-line therapy and 55% had a single site of progression. Enrollment was limited to patients with ≤ 3 sites of progression in $\leq 30\%$ of all metastases, which was a more restricted definition of oligoprogression than the ESTRO-EORTC definition [7]; IMDC poor-risk patients were also excluded. The study exceeded the threshold for its primary end point of >6 months freedom from changing systemic treatment in $>40\%$ of patients, as 70% (CI: 45%–85%) of the cohort was able to continue therapy due to SABR MDT. With median follow-up of 10 months, 30% of patients received additional sequential SABR to new sites of oligoprogression. SABR provided 100% LC and extended the median time to next-line systemic therapy (or death) to 11 (CI: 5–19) months was used. One patient had grade 3 toxicity (colitis and bowel perforation) while receiving lenvatinib and everolimus 5 months after treatment of two nearby abdominal radiation targets. At 3 months after MDT, quality-of-life scores showed no changes from baseline. This trial extended the Cheung trial by enrolling patients on immunotherapy and combination therapy.

One of the challenges in treating oligoprogressive disease with SABR is the risk of cumulative toxicity between escalated ablative radiation doses and ongoing systemic therapies. Some targeted therapies increase the risk of potentially severe complications from SABR, while immune therapies have side effect profiles that overlap additively and sometimes synergistically with radiation toxicity profiles. The ESTRO-EORTC OligoCare consortium recently summarized data on the safety of SABR with concurrent targeted and immune therapies and reported consensus recommendations to mitigate risks of in-field grade 3+ toxicities, including duration of holding systemic therapy before and after SABR, omission of planned infusion cycles, avoidance of same-day treatment overlap and SABR dose reduction [92]. For VEGFR-TKIs, there was consensus or majority opinion to hold therapy for up to 2 weeks, with concurrent sorafenib specifically associated with $>20\%$ of severe toxicity for hepatic targets, but no increased toxicity seen for osseous targets. This caution is supported by a recent meta-analysis of toxicity from concurrent VEGFR-TKIs with radiation [93]. Consensus for anti-PD-1/PD-L1 ICI monotherapy was to avoid omission of any infusion cycles during concurrent SABR, but no majority was reached for a minimum safe period between

infusions and SABR, with 0–10% risk of severe toxicity. For the CTLA-4 inhibitor ipilimumab, the majority agreed to hold therapy >1 week, as treatment of thoracoadominal locations was associated with severe toxicity in 10–20%. For dual immunotherapy (ipilimumab/nivolumab), there was consensus to hold therapy for >1 week, with concurrent SABR associated with severe thoracic toxicity in >20%. Consensus was to omit >1 bevacizumab cycle and avoid therapy for >1 week due to 11–20% risk of severe toxicity for abdominal targets. The majority suggested to avoid same-day treatment overlap or SABR dose reduction, except for temsirolimus and everolimus, for which there was consensus only to avoid SABR dose reduction. Prospective investigation of dosimetric data linked to outcomes is needed to better understand and mitigate in-field and out-of-field toxicities associated with radioimmunotherapy.

7.3. Thermal ablation

The only prospective study of thermal ablation for oligometastatic or oligoprogressive disease to our knowledge was reported by Campbell et al, who conducted a Phase I evaluation of cryotherapy to a single oligometastatic focus with a CTLA-4 inhibitor versus the CTLA-4 inhibitor alone in 29 patients [94]. With median follow-up of 29 months, one patient had a radiographic response after cryotherapy; 1 patient in the combined modality arm and 2 in the immunotherapy-only arm stopped immunotherapy without requiring additional systemic therapy. The overall rate of grade 3+ toxicity was 55% (similar in both arms) and toxicity led to treatment discontinuation in 35% overall (5 patients in each arm).

For lung metastases, three prospective studies addressed the safety of thermal ablation and included small RCC cohorts. The only study to report histology-specific outcomes was a multicenter observational study of LC after radiofrequency ablation in 566 patients with 1037 lung metastases treated between 2002–2010 [95]. For the 68 (12%) patients with RCC, LC was 93% at 1 year and 75% at 3 years. The risk of pneumothorax in the overall cohort was 67%, and 58% required chest tubes. Real-world data suggest 32% of cryoablation treatments incur chest tubes, and 6–12% have major complications across thermal ablation modalities [33].

7.4. Patient selection for metastasis-directed therapy

Potential factors to guide the selection of patients for MDT of distant metastases include good performance status, low-volume disease, good response to upfront systemic therapy, a long disease-free interval for

metachronous disease and the patient-specific benefits of avoiding the start of or changing systemic therapy. A national study of utilization trends suggests that resection is more common for lung and adrenal metastases, while radiotherapy is more utilized for bone, lymph, liver and CNS disease [96]. Patients who receive surgical metastatectomy often have good performance status, a low burden of disease and favorable risk features, so surgical selection bias may limit generalizability, and there are no validated selection criteria for resection. Radiation therapy may be preferred for inoperable or unresectable disease, foci with high surgical morbidity such as CNS or bone disease, or multiple foci, due to effective control without the morbidity of (multiple) surgical resections. In some cases such as osseous or epidural spine disease, combined modality treatment, involving maximal safe resection or decompression followed by adjuvant ablative radiotherapy, is appropriate [28].

Given the paucity of evidence on the efficacy and safety of thermal ablation, multidisciplinary discussion with representatives from urologic, medical and radiation oncology as well as interventional radiology may improve patient selection and outcomes. With higher-quality evidence, percutaneous and catheter-based ablative techniques may become important tools for the significant minority of patients whose disease is not amendable to (repeat) non-invasive ablative radiotherapy because of prior radiation, disease location, comorbidities, or availability of technology and expertise. Careful patient selection is necessary to minimize the risks associated with anesthesia, bleeding and intravenous contrast as well as potential procedural complications. Comparative prospective evaluation of relative benefits and toxicity and collaborative prospective registries to collect data on long-term outcomes are warranted.

The lack of high-quality data is reflected in discrepant guidance on the optimal MDT modality. While the Latin American multidisciplinary guideline limits routine surgical metastasectomy to patients with IMDC favorable-risk disease, a single site of extracranial disease, and more than a year from nephrectomy to metastatic disease for metachronous disease and does not discuss non-surgical MDT [30], other guidelines consider MDT with surgery or SABR for all risk groups with oligometastatic and oligoprogressive disease, without a clear consensus on specific techniques across guidelines. European guidelines consider surgery the default modality and consider SABR when invasive techniques are not appropriate or excessively morbid [21,23]. North American guidelines generally recommend SABR and thermal ablation alongside surgery for both oligometastatic and oligoprogressive scenarios [16,25,29], while the American Society of Clinical Oncology (ASCO) favors SABR over surgery for

oligoprogressive disease due to the lower morbidity and easier intercalation with systemic therapy [16]. Notably, the Pan-Asian adapted ESMO guidelines do not discuss the role of MDT outside of palliation [26].

Additional society guidelines address management of bone, lung and CNS metastases. For osseous disease, the IKCC/German Cancer Society renal working group guidelines on bone metastases recommend either wide surgical resection alone, or multimodal treatment with surgery and adjuvant SABR as preferred options, with consideration of thermal ablation for small lesions [28]. CIRSE has published general guidelines on patient selection and procedural techniques for thermal ablation of oligometastatic bony disease; potential advantages compared with external radiation or surgery include lower risks incurred by multiple treatments to the same site [19]. For lung metastases, multidisciplinary consensus recommendations endorsed by CIRSE suggest that ablation may be considered alongside other MDT modalities, with ideal candidates having small unilateral tumors [18,33]. Although most guidelines recommend palliative whole-brain radiotherapy for high volume CNS disease, stereotactic radiosurgery (SRS) should be considered when possible, to minimize interruptions to systemic therapy and the risk of cognitive side effects. The ESTRO-EORTC definition of oligometastatic disease [7,97] and the prospective studies of SABR for oligo-RCC discussed above excluded patients with brain metastases. However the ESTRO-American Society for Radiation Oncology (ASTRO) consensus definition of oligometastatic disease limits the number of extracranial oligo-foci only by the ability to deliver definitive-intent treatment to all sites of disease [97]. Optimal patient selection for focal treatment in terms of the number, size and velocity of brain metastases, the interplay of CNS-penetrative systemic therapy and intracranial focal therapy and the relationship between aggressive focal treatment of CNS disease and overall outcomes is unclear and should be addressed by future research.

8. Follow-up after cytoreductive or metastasis-directed therapy

Prospective trials of SABR for oligo-disease typically specify surveillance with CT body imaging every 3 months and assess response with RECIST [88–91,98–100]. For all patients with metastatic disease, interval history, exam and body imaging with RECIST evaluation is recommended every 1–4 months across guidelines. ASCO recommends close follow-up including serial bone and CNS imaging after MDT [16], but in general CNS imaging, preferably with MRI with contrast, is recommended as clinically indicated. There is no high-quality data compar-

ing different follow-up intervals during systemic therapy, the incidence and pattern of progression during or after systemic therapy, or outcomes after immediate versus delayed treatment of asymptomatic new or progressive metastatic sites. Notably, there is no evidence that radiologic progression should mandate stopping or changing treatments.

The benefit of continuing systemic therapy after surgical or ablative MDT to all sites of disease is unclear. The EAU weakly recommends cautious consideration of adjuvant pembrolizumab for oligometastatic patients with no active disease after MDT [22] based on the results of KEYNOTE-564 [101], while ESMO considers it an option [24], Canadian guidelines recommend against it in the absence of OS benefits [29] and other guidelines do not discuss it. The prospective trials RAPPORT and NIVES support that adjuvant single-agent immunotherapy following SABR is adequately tolerated in carefully selected patients [98,100].

9. Conclusion

Focal management options for oligometastatic and oligoprogressive RCC are evolving. The role of cytoreductive nephrectomy has been questioned by changes in systemic therapy, stereotactic ablative radiotherapy is an emerging alternative for primary and distant disease, and other ablative techniques represent a new frontier. Optimal patient selection for focal treatment techniques is challenging and multidisciplinary discussion of management options should be considered. Ongoing studies may improve patient selection for focal therapy prior to systemic therapy and for distant oligometastatic or oligoprogressive disease.

10. Future perspective

The need for durable and safe focal treatment options for oligometastatic and oligoprogressive RCC has grown, but several gaps limit optimal patient selection for cytoreductive or metastasis-directed therapy. First, better prognostic tools, potentially including advanced imaging techniques, tumor genomic testing and serologic or urine biomarkers, are needed to risk stratify patients along the oligo-disease spectrum. Second, the benefits of cytoreductive treatment in patients receiving combination immunotherapy should be clarified in a prospective fashion. Third, focal treatment of distant metastases needs further investigation to elucidate optimal patient selection factors, treatment techniques and timing with systemic therapies to better understand survival and cost benefits and patient-reported outcomes. Patients should be enrolled on prospective randomized trials with clinical

equipoise when feasible. Ongoing studies of focal therapy are summarized in Table 2.

Article highlights

Evaluation

- Oligometastatic and oligoprogressive renal cell carcinoma (RCC) should be evaluated with contrast-enhanced body CT and brain MRI, with additional imaging based on symptoms or as needed for planning of future focal treatments. Guidelines stratify patients by International Metastatic RCC Database Consortium (IMDC) prognostic risk groups (section 4).

Management

- While the quality of the data is mixed, there are myriad options for treating oligometastatic and oligoprogressive RCC, including active surveillance, systemic therapy, focal cytoreductive treatment of the primary and focal metastasis-directed therapy. Optimal patient selection, timing and choice of focal therapy in contemporary clinical practice remains unclear. Discussion of management options for metastasis-directed therapy including surgery, stereotactic ablative radiotherapy and thermal ablation should be discussed in a multidisciplinary setting (section 7).

Follow-up after focal therapy

- After focal treatment of metastatic disease, current guidelines recommend CT body imaging every 1–6 months with annual history and physical for 5 years. There are no high-quality data on the benefits of systemic therapy after focal treatment of all sites of metastatic disease (section 8).

Future directions

- Multiple ongoing trials are investigating the optimal choice, timing and combination of focal treatment techniques with immunotherapy for oligometastatic and oligoprogressive RCC (section 9).

Author contributions

AC Anderson contributed to the conception, design and planning of the study; acquisition of data; analysis of data; interpretation of results; drafting the manuscript; critically reviewing or revising the manuscript for important intellectual content. J Tsai and SS Lo contributed to the conception, design, or planning of the study; and critically reviewing or revising the manuscript for important intellectual content. All authors contributed to interpretation of the results and critically reviewing or revising the manuscript for important intellectual content.

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