Oncology, Nuclear Medicine and Transplantology
(eISSN 3105-8760)

Review Article

Surgery in Metastatic Disease: When Is It Justified?

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Received: May 21, 2026
Accepted: Jul 07, 2026

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Citation: Josiah PA, Nkemdilim JA. Surgery in Metastatic Disease: When Is It Justified?. Oncology, Nuclear Medicine and Transplantology. 2026;2(3):onmt021. https://doi.org/10.63946/onmt/18956

ABSTRACT

Surgery in metastatic cancer has been considered to have a limited role in the treatment of metastatic disease and has generally been reserved for palliative intent. However, as imaging, systemic therapy, surgical techniques, and understanding of the biology of cancer has improved, the role of surgery in the treatment of metastatic disease has evolved. This narrative review will discuss the current state of surgical therapy in metastatic cancer and the indications for such an approach. A discussion of the impact of reducing tumor burden, the concept of oligometastatic disease, and the role of host–tumor interactions will provide a basis for the discussion. The objectives of surgery have evolved from palliation to include longer survival and even potentially curative intent. The primary consideration in the decision to pursue surgical therapy for metastatic disease is proper patient selection, and this requires a thorough evaluation of disease and patient factors, as well as the integration of systemic therapy and other local therapies. While evidence is strongest for metastasectomy in colorectal cancer, there is growing evidence in breast cancer, renal cell carcinoma, lung cancer, and neuroendocrine tumors. As a general rule, the optimal management of metastatic cancer includes a combination of systemic and surgical therapies to maximize benefit for the patient. While there are limitations to the current role of surgical therapy in metastatic cancer, challenges including surgical morbidity, delays in initiation of necessary systemic therapy, and a paucity of high-quality evidence, proper patient selection remains the cornerstone to providing meaningful clinical benefit.

Keywords: Metastatic Cancer; Metastasectomy; Oligometastatic Disease; Tumor Burden; Patient Selection

Introduction

Metastatic cancer, or cancer that has spread from its origin to other parts of the body, is responsible for the majority of cancer related deaths around the world [1]. The perception that metastatic cancer is invariably incurable, has dominated cancer management, guiding traditional strategies which focused on prolonged survival and symptom control. Historically, surgical therapy in the metastatic setting was typically viewed as having little to no role in the curative management of such cases and was usually reserved for the purpose of palliation to address specific complications of cancer, such as tumor obstruction, catastrophic hemorrhage, or pathological fractures. The notion existed that once a cancer began to metastasize it became incurable [2,3].

This approach of management utilized systemic therapy and radiotherapy as primary treatments. Chemotherapy, hormone therapy and more recently targeted therapy was used to control widespread disease. Radiotherapy was used to control local symptoms and to treat local disease. Surgery was not widely used due to concerns regarding patient morbidity and delay to initiation of systemic therapy, with many practitioners sharing the belief that even if a patient were a surgical candidate, resection would not alter the natural history of metastatic cancer [4,5].

Management strategies for patients with metastatic disease have undergone dramatic evolution over the past two decades. Improved imaging, including high resolution computed tomography and magnetic resonance imaging, as well as identification of metastatic sites via positron emission tomography and molecular imaging, now permit accurate determination and quantification of metastatic disease burden, facilitating precise patient stratification [6]. Advances in anesthesia, perioperative care, and surgical techniques including minimally invasive and robotic approaches have all contributed to lowering the risks associated with surgical therapy and expediting recovery in postoperative patients. As a result, patients that were previously not surgical candidates can now be offered curative intent surgery [7].

Recent advances in targeted therapies and immunotherapies have led to lasting remissions and long survival in patients with metastatic cancer. These findings have refocused attention on the place of surgical intervention as part of a comprehensive treatment strategy for cancer. The oligometastatic patient, with a limited burden of disease, exemplifies one such scenario in which curative intent surgical therapy is now indicated as part of overall patient management [8,9].

While progress has been observed in this field in terms of patient management, clinicians are still faced with the more difficult clinical problem of weighing the advantages of surgery against the potential risks in patients with advanced cancer, whether these involve longer or curative survival, relief of unpleasant symptoms, or a general improvement in quality of life [10].

In this review the role of surgery in metastatic disease will be evaluated and the clinical situations where its application can be advocated on evidence will be defined. This analysis should provide oncologists with a sound framework upon which to base current surgical decisions.

Methodology

This narrative review examines the role of surgery in metastatic disease. Literature searches were conducted in PubMed, Google Scholar, and ResearchGate using combinations of terms such as “metastasectomy,” “cytoreductive surgery,” “oligometastatic disease,” “surgery in metastatic cancer,” and tumor-specific keywords (e.g., colorectal liver metastases, cytoreductive nephrectomy). Reference lists of retrieved articles, clinical practice guidelines, and key review articles were also hand-searched to identify additional relevant studies.

The literature considered for inclusion primarily encompassed studies published from the early 2000s through 2025, with particular emphasis on contemporary evidence reflecting advances in systemic therapy, molecular oncology, immunotherapy, and multidisciplinary cancer care. Landmark earlier studies were included when they established foundational concepts or substantially influenced current surgical practice.

Relevant English-language peer-reviewed publications, including randomized controlled trials, meta-analyses, systematic reviews, prospective and retrospective cohort studies, and consensus statements, were considered. Although a formal hierarchy of evidence was not applied, priority was given to higher-level evidence where available, particularly randomized trials, prospective studies, major guidelines, and large meta-analyses. Retrospective studies were included in areas where prospective evidence was limited or unavailable, reflecting the nature of the surgical oncology literature.

Data were synthesized narratively, with findings interpreted in the context of study design, sample size, methodological limitations, potential sources of bias, consistency of results across studies,

and relevance to contemporary oncologic practice. Particular attention was given to areas of controversy where randomized and observational evidence have yielded differing conclusions, as well as to emerging evidence that may influence future surgical decision-making in metastatic disease. No formal systematic review protocol was followed.

Biological Rationale for Surgery in Metastatic Disease

The role of surgery in metastatic cancer has evolved based on our increased understanding of metastatic tumor biology, disease kinetics, and host–tumor interactions. Although metastatic cancer by definition is a multisystem disease with widespread dissemination, the biology of the disease is not uniform and, consequently, some metastatic cancer may be amenable to local control with curative intent [11,12].

Tumor Burden and Disease Kinetics

A key determinant of disease progression and response to therapy in metastatic cancer is the amount of tumor present at diagnosis. Tumor debulking is a strategy where an attempt is made to reduce the volume of cancer present in order to change the kinetics of the disease and improve response to subsequent therapy. High tumor burden is associated with more aggressive disease, with higher levels of genomic instability, greater degree of immunosuppression, and worse patient outcomes in multiple cancer types [13].

The goal of reducing the size of a tumour (debulking) allows chemotherapy to be more effective by two mechanisms. Firstly, by reducing the burden of tumour that needs to be treated, the amount of cancer to be killed by chemotherapy is lessened, which in itself can increase the therapeutic index of the drugs used. Secondly, the metabolic changes that a large tumour places on the host are greatly reduced, meaning that many of the toxic cytokines normally produced in large amounts by a tumour are no longer produced. The decrease in growth factor production also means that many of the host's immune responses that are inhibited by the tumour are reduced. Such combinations of surgical therapy with systemic therapy have a biological rationale, and in many cases have been shown to provide marked survival benefits for patients with malignancies [14,15].

The Oligometastatic Disease Concept

Oligometastatic disease refers to a distinct biological state of cancer characterized by the existence of a limited number of metastatic lesions, usually confined to single organs or a few organs. Originally conceptualized as an "oligometastatic state" as an intermediate stage between localized disease and widespread metastatic disease, oligometastatic disease is thought to represent a disease with limited potential for metastasis and with "slow-growing" tumor biology. The concept has evolved to include the notion that an aggressive local treatment approach to all known sites of disease can result in long durations of disease-free survival and, rarely, long-term survival [12,13].

Oligometastatic disease should be distinguished from oligoprogressive disease and polymetastatic disease. Oligoprogressive disease refers to the occasional progression of a few lesions while the majority of lesions continue to respond to targeted therapy and remain under control systemically. Polymetastatic disease refers to the early widespread dissemination of cancer at the time of diagnosis. Importantly, the potential benefit of oncologic surgery and other forms of localized therapy to control oligometastatic disease decreases markedly as the patient's burden of disease increases and as the underlying disease becomes more aggressive [15,16].

Tumor–Host Interactions

While focus has long been given to the bulk and distribution of the tumour load, the interaction of the tumour with the host immune system plays a critical role in determining the clinical behaviour of the disease. By removing tumour tissue, surgery has the potential to influence the immune system, reducing sources of immunosuppression and decreasing systemic and local inflammation. There is growing interest in how surgery might 'normalise' the tumour microenvironment allowing greater effectiveness of immunotherapy. While postoperative immunosuppression is undoubtedly a feature in the immediate postoperative period, in carefully selected patients the overall effect is generally positive and even enhanced by addition of modern systemic therapies [12,13].

From a biological point of view, it is easy to justify the role of surgery in metastatic disease when it is properly integrated into a multidisciplinary approach.

Goals of Surgery in Metastatic Disease

The goals of surgery for metastatic cancer are not simply limited to a curative intent in the rare circumstance that it might be possible, versus palliation in all other cases. In reality, surgery in the metastatic patient has multiple purposes that may overlap. The objectives are often diverse and always hopeful, aiming for long-term survival in highly select patients, symptom relief, and prevention of life threatening

complications. Therefore, it is paramount that the objectives of surgical intervention be well understood. The surgeon and patient must have a clear and common understanding of goals, so that appropriate patients are selected, realistic expectations are provided, and outcomes are properly assessed [3,17,18].

Curative Intent

Although rarely the case, the possibility of curative-intent treatment of metastatic cancer is a realistic goal in selected cases. The complete resection of isolated liver or lung metastases from patients with colorectal cancer is the most well established example of an apparent cure of metastatic cancer. The likelihood of a good or even permanent result is related to several factors including the presence of limited disease, indolent disease biology, and the potential for complete resection (R0) [17,18]. It is critical that all appropriate staging evaluations be completed to determine whether occult sites of metastatic disease are present. The combination of clinical evaluation, imaging, and appropriate use of neoadjuvant or postoperative adjuvant chemotherapy allows for the optimal patient selection for surgical therapy of metastases. The select cases, where cure of apparently intractable metastatic cancer was possible, challenged the standard consideration of metastatic cancer as incurable. A thoughtful, individualized approach to each patient with metastatic cancer is critical for optimal outcomes [18,19,20].

Survival Prolongation

Surgery in most cases is not curative but can extend survival with meaningful quality of life. Cytoreductive surgery can downstage disease, making subsequent therapy more effective, and temporize until definitive treatment can be undertaken. This strategy has demonstrated survival benefit in patients with various malignancies, including advanced stage ovarian cancer and renal cell carcinoma, who undergo cytoreductive surgery followed by or in conjunction with medical therapy. The timing and sequence of surgery in relation to medical therapy is crucial, and the risks of poor timing may far outweigh any potential benefits of the surgery [20,21].

Palliation

Palliative surgery is one of the most common indications for surgical intervention in patients with metastatic disease. The goals of surgery in these patients are to alleviate serious and life-altering symptoms (such as severe pain, intestinal obstruction, uncontrollable hemorrhage, or severe neurological dysfunction) that are severely impairing a patient's quality of life. Although every surgical procedure carries inherent risks of morbidity and mortality, the measure of palliative surgery success is the degree of relief from the patient's most troubling symptoms, improvement in performance status, and a patient's self-reported quality of life [3].

Diagnostic and Preventive Indications

Surgery is not limited to the treatment of symptoms of metastatic cancer. It can also serve as a diagnostic or preventative procedure to treat patients. Diagnostic surgery can obtain tissue for histopathologic examination, to carry out molecular studies or to measure biomarkers that will guide the use of a targeted or an immunotherapy. Preventive surgery can forestall catastrophic events such as impending pathological fracture, spinal cord compression, or major vessel erosion. In such cases, even with limited survival, major benefits can be obtained through the prevention of severe or life-threatening morbidities, such as continued independent function, prevention of pathological fracture, or repair of life-threatening hemorrhage [22,23]. Figure 1 shows the goals of surgery in Metastatic disease.

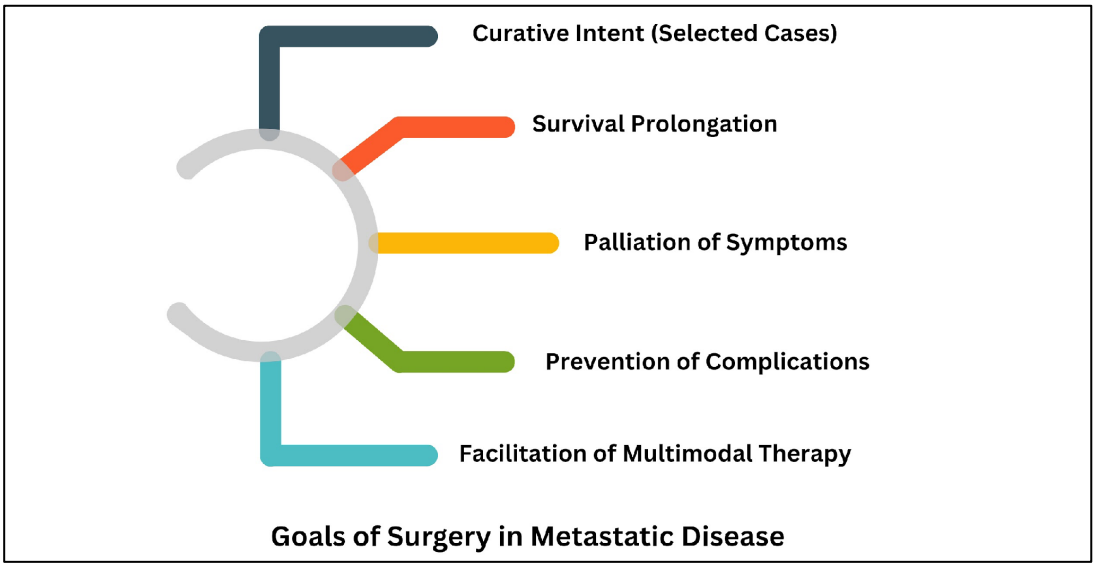

Figure 1: Conceptual Model of Indications and Goals of Surgery in Metastatic Cancer

Patient Selection: Who Benefits from Surgery?

Patient selection is critical in the surgical management of metastatic disease. Surgery is inherently risky, and the biological and clinical behavior of metastatic cancer is extremely variable. Hence, a balanced assessment of the benefits versus the risks in the individual case is critical. Decisions to undertake surgical intervention must therefore not be made routinely or as a default option, but rather as a result of individualized and evidence-based consideration and within the context of multidisciplinary management [24-27].

Disease Factors

The potential benefit of metastasectomy or cytoreductive surgery for an individual patient is mainly determined by the disease characteristics. The number, size and distribution of metastases (e.g. few lesions vs. multiple lesions; limited to one organ vs. multi-organ dissemination) are critical in this respect. Most important is the difference between limited and diffuse disease. Additionally, the specific anatomic site of metastasis is important because resectability, surgical complexity and perioperative risk all differ for lesions in different organs (e.g. liver versus brain versus bone) [26,28].

The "disease-free interval" is defined as the length of time between the completion of definitive therapy for the primary tumor and the diagnosis of metastatic disease. This time interval is a surrogate marker of tumor behavior and biology, and generally longer intervals are associated with more indolent disease and improved patient outcomes with surgical resection, whereas more rapid or synchronous progression of metastatic disease is associated with highly aggressive disease and poor patient outcomes with local therapy [25,26,29,30].

Consideration of molecular and biological features in decision making has become increasingly important. Recent advances in the field of genomic profiling have identified significant tumour heterogeneity, even within the same metastatic site. Identification of 'favourable' biology, such as low clonal diversity, microsatellite instability or presence of an actionable mutation, suggests that many patients may derive substantial benefit from aggressive local therapy. Conversely, highly aggressive tumours or those that are highly unstable genomically typically have little to no benefit from surgical therapy, even when technically resectable [29].

Patient Factors

Importantly, patient-specific factors may play an equal role in decision-making as the tumor biology itself. Factors such as performance status, whether measured by ECOG score or WHO performance status, help predict surgical risk, postoperative recovery, and long-term survival. Good performance status indicates a better candidate than a patient with poor performance status [31,32]. An evidence-based framework summarizing these key decision points is presented in Figure 2, illustrating a practical approach to individualized surgical decision-making in contemporary oncologic practice.

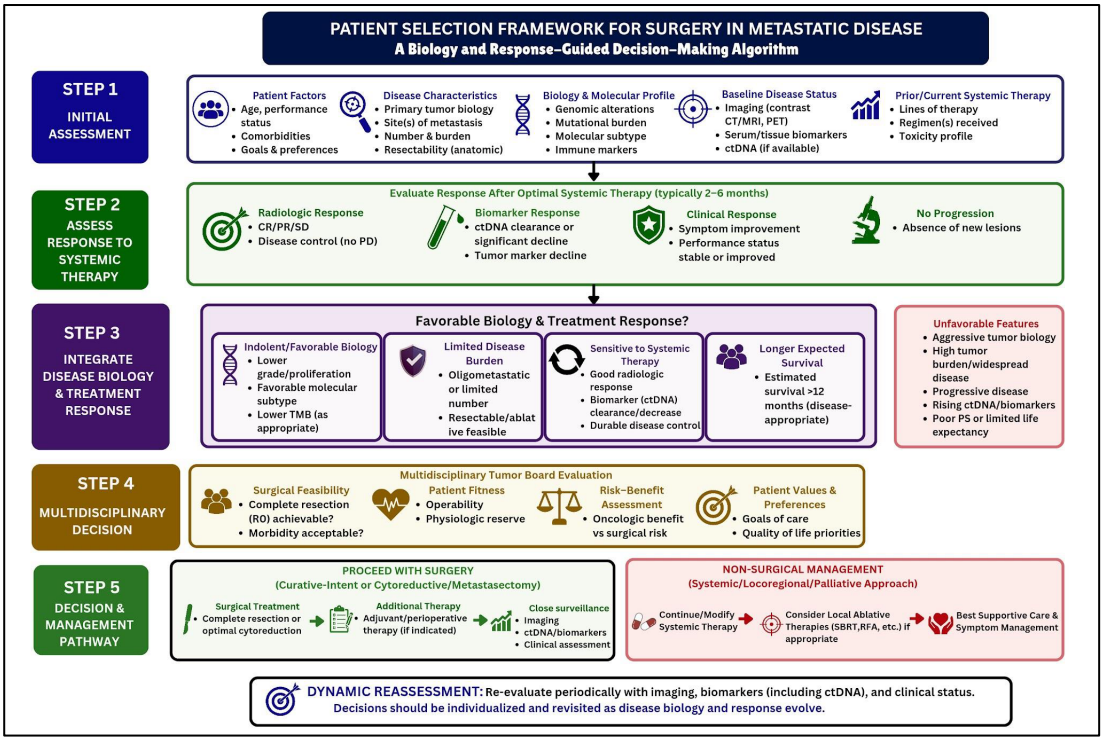

Figure 2: Precision-Based Patient Selection Algorithm for Surgical Management of Metastatic Disease

The same thorough consideration must be given to a patient's medical co-morbidities and estimated life expectancy when deciding whether to recommend major surgery. In patients with severe organ dysfunction or very limited life expectancy, major surgery is unlikely to provide any meaningful benefit over less invasive approaches that can manage a patient's symptoms. Importantly, the patient's values and priorities, including their acceptance of risk, must drive the surgical decision-making process. A thorough discussion of the expected outcomes, potential trade-offs, and impacts on a patient's quality of life — even in situations with incomplete or uncertain evidence — is critical when weighing these important considerations [27,31,32].

Treatment-Related Factors

Selection of patients for metastasectomy also depends on other factors related to the overall treatment plan and course of care for the patient. One of the strongest predictors of benefit from metastasectomy is response (or disease stabilization) on systemic therapy. Patients whose disease is controlled or induced to remission with medical therapy are more likely to benefit from resection of metastatic disease than are those with ongoing disease progression on chemotherapy [29].

Access to genuine multidisciplinary expertise to optimize management and decision-making for each patient is mandatory. While the surgeon/oncologist plays the pivotal role, full-team participation of other disciplines, including medical, radiation, interventional radiology, pathology, and palliative oncology disciplines, is necessary. Importantly, the expected surgical risk must be weighed against anticipated therapeutic objectives (survival, local control, symptom relief, or risk avoidance in face of unresectable liver disease) in order to ensure the indicated surgical approach is congruent with overall patient management [27,33].

Table 1: Core Considerations for Surgical Decision-Making in Metastatic Disease

Domain	Key Factors	Clinical Relevance
Disease Factors	Number, size, and distribution of metastases; site; disease-free interval; tumor biology	Limited, indolent, and resectable disease favors surgery
Patient Factors	Performance status, comorbidities, frailty, life expectancy, patient preferences	Determines operative risk, recovery, and alignment with goals
Treatment Factors	Response to systemic therapy; timing; alternative therapies	Guides selection and sequencing of surgery within multimodal care
Surgical Factors	Resectability (R0), complexity, morbidity risk	Defines feasibility and potential benefit of intervention
Oncologic Goals	Curative intent, survival prolongation, palliation, complication prevention Clarifies purpose and expected outcomes of surgery	Clarifies purpose and expected outcomes of surgery
Multidisciplinary & Ethical Considerations	Tumor board input; shared decision-making; risk–benefit balance	Ensures patient-centered, evidence-based decisions

Evidence by Primary Tumor Type

The role for surgery in the management of metastatic disease is primarily determined by the biology of the primary tumour, its pattern of metastasis and sensitivity to chemotherapy. While there is substantial evidence to support a role for surgical therapy in some tumour types, others remain undefined or are of limited benefit except under select circumstances [12,29]. This section reviews the current evidence for major tumour types in which surgery in the setting of metastatic disease has been most extensively evaluated.

Colorectal Cancer

Metastasectomy for colorectal cancer (CRC) is the most supported indication for surgery for metastases. Liver metastases develop in up to 50% of patients with CRC during the course of their disease. Complete surgical resection (R0 resection) of these metastases has become a standard treatment for selected patients with colorectal liver metastases. Results from large institutional series and from case series and registries from different countries show 5-year overall survival rates of 40% to 60% after an R0 hepatectomy, which exceeds the results of patients undergoing systemic therapy. Although the level of evidence is low because of the lack of sufficient randomized controlled trials, metastasectomy of liver metastases is considered standard treatment for fit patients with resectable disease and limited extrahepatic disease [34,35].

The randomized EORTC 40983 trial provided quantitative support for multimodal management of resectable colorectal liver metastases. Among patients with up to four resectable liver metastases, perioperative FOLFOX4 chemotherapy improved 3-year progression-free survival by approximately 7–9% compared with surgery alone, with hazard ratios ranging from 0.73 to 0.79 across analyzed populations. However, perioperative chemotherapy was associated with a higher rate of reversible postoperative complications (25% versus 16%), emphasizing the need to balance improved disease control against treatment-related morbidity [36]. In addition to liver metastases, pulmonary metastasectomy is also performed for patients with colorectal cancer, particularly those with limited lung disease and control of the primary disease. In selected patients, 5-year survival rates have approached 30–50%. Although most studies are retrospective, and the issue of whether the observed survival benefits truly reflect an antitumor effect of resection or simply patient selection remains open to debate, the trend supports the continued, cautious application of pulmonary metastasectomy for select patients. This controversy was highlighted by the PulMiCC randomized controlled trial. Although the study was underpowered because of poor accrual and early closure, it challenged the long-standing assumption that pulmonary metastasectomy confers a substantial survival advantage. Importantly, survival among non-operated patients was considerably better than historically expected, suggesting that favorable outcomes reported in retrospective surgical series may partly reflect selection bias rather than treatment effect. Subsequent analyses of the trial emphasized that, despite limited statistical power, the findings undermine the widely held belief that pulmonary metastasectomy produces a major survival benefit in all eligible patients. Consequently, the true magnitude of benefit remains uncertain and warrants continued evaluation in the context of modern systemic therapies [37]. Recurrence after metastasectomy remains a significant issue, emphasizing the importance of effective perioperative systemic therapy and life-long follow-up [36,37].

Breast Cancer

Surgery for stage IV breast cancer continues to be a subject of debate. Initially, the role of surgery for the primary tumor in patients with metastatic disease was to control local symptoms such as bleeding, ulceration, or fungation from large tumors. Improved survival for patients with stage IV breast cancer following surgery for the primary tumor was suggested in several retrospective studies. As a result, several prospective randomized trials have been conducted, and the results are mixed. The conflicting findings of randomized trials illustrate the ongoing controversy regarding surgery in de novo metastatic breast cancer. In the Tata Memorial trial, locoregional treatment of the primary tumor did not improve overall survival, with median survival of 19.2 months in the surgery group compared with 20.5 months in the non-surgical group (HR 1.04, 95% CI 0.81–1.34). In contrast, the MF07-01 trial reported a 34% reduction in mortality risk among surgically treated patients (HR 0.66, 95% CI 0.49–0.88), with apparent benefit concentrated among younger patients, those with hormone receptor-positive disease, HER2-negative tumors, and solitary bone metastases. These divergent findings suggest that any survival advantage from surgery is unlikely to be universal and may depend heavily on patient selection, disease biology, and metastatic burden. As systemic therapies continue to improve, surgical intervention is increasingly viewed as an individualized strategy rather than a routine component of treatment [38,39].

Subgroup analyses from these studies and other observational data suggest that some patients may be candidates for surgical treatment of the primary tumor. Examples of patients who may be candidates for surgical treatment include those with hormone receptor–positive cancer, those with low burden of metastatic disease, those with bone-only metastases, and those who have an excellent response to first-line systemic therapy. In contrast, those with triple-negative biology, those with visceral-dominant disease, and those with rapidly progressing metastatic disease are unlikely to benefit. The decision for surgery in patients with metastatic breast cancer should therefore be highly individualized and made after careful consideration, within a multidisciplinary team, of the degree of systemic disease control that can be achieved [38,39].

Renal Cell Carcinoma

Cytoreductive nephrectomy (CN) was traditionally incorporated into the management of metastatic renal cell carcinoma (mRCC) and provided a clear benefit to overall survival, especially during the cytokine era. However, the advent of targeted therapy and immune checkpoint inhibitors has profoundly impacted the role of CN in mRCC. The findings from two randomized clinical trials, CARMENA and SURTIME, have demonstrated that patients with intermediate- or poor-risk features or with high metastatic volume do not benefit from upfront CN when receiving contemporary systemic therapy [40,41]. These trials represent a major shift in the management of metastatic renal cell carcinoma because they challenged conclusions derived from decades of retrospective evidence. The CARMENA trial demonstrated that sunitinib alone was not inferior to nephrectomy followed by sunitinib in intermediate- and poor-risk patients, with median overall survival of 18.4 months versus 13.9 months, respectively. Similarly, SURTIME reported no progression-free survival advantage with immediate nephrectomy and suggested improved overall survival with deferred nephrectomy following initial systemic therapy (median overall survival 32.4 versus 15.0 months; HR 0.57, 95% CI 0.34–0.95). Together, these studies emphasize the importance of candidate selection and systemic disease control before surgery. However, interpretation of these trials must consider that both were conducted in the targeted therapy era, whereas current treatment paradigms increasingly rely on immune checkpoint inhibitor–based combinations. Consequently, the optimal role and timing of cytoreductive nephrectomy remain active areas of investigation [40, 41].

Recently, the approach has shifted to an initial approach of upfront systemic therapy, with surgical therapy being considered for patients who demonstrate a good response to systemic therapy or have a long period of stable disease. Timing, patient risk stratification, and response to systemic therapy are key considerations when trying to determine whether surgical therapy can provide additional benefits in patients with metastatic RCC [41].

Non–Small Cell Lung Cancer

The role of surgery in non–small cell lung cancer (NSCLC) has evolved, and one of the few circumstances in which surgical resection remains indicated is in the setting of oligometastatic disease. Patients found to have a solitary or limited number of metastases (most commonly to the brain or adrenal gland) can achieve significant gains in both progression-free and overall survival from local therapy for their metastases (surgical metastasectomy or stereotactic ablative radiotherapy) in conjunction with resection of their primary tumor. Although randomized data is lacking, data from prospective studies and cancer registries support intervention in well-selected patients [42]. Quantitative evidence supporting local consolidative therapy was provided by Gomez and colleagues, who demonstrated a significant improvement in progression-free survival among patients with three or fewer metastatic lesions who had not progressed after first-line systemic therapy. Median progression-free survival increased from 3.9 months in the maintenance therapy/observation group to 11.9 months in the local consolidative therapy group (HR 0.35, $p = 0.0054$). Although the trial was terminated early after demonstrating efficacy, the findings provided important prospective support for aggressive local treatment in carefully selected oligometastatic patients [42].

Advances in systemic therapies (targeted therapy and immunotherapy) have further refined the process of biological and clinical stratification and treatment timing. With these advances, surgery is typically performed after control of disease with systemic therapy or in the setting of true oligometastases [42].

Neuroendocrine Tumors

Neuroendocrine tumors (NETs), especially well-differentiated varieties, have a unique indolent natural history and can present with symptoms attributable to hormonal hypersecretion. Resection of the primary tumor is recommended for midgut and pancreatic NETs, regardless of the presence of unresectable liver metastases. In addition to providing potentially durable relief from symptoms, curative or partial resection of the primary tumor can prevent complications such as bowel obstruction or necrosis, decrease hormonal production and in selected patients, surgical resection has been shown to result in improved survival [43].

Decisions regarding operation are based on tumor grade, patient function, resectability of the primary tumor, and burden of metastatic disease. Debulking of liver metastases can also result in a major quality of life improvement for patients with functional tumors in whom complete resection is not possible [42].

Other Tumors

Selected patients with metastatic melanoma can achieve long-term remission or durable disease control following complete metastasectomy. Not only has complete metastasectomy been shown to potentially cure patients with metastatic melanoma but with the advent of effective immunotherapy and targeted therapy, selected patients may now attain long-term remission or durable disease control [44]. In

addition to patients with metastatic melanoma, pulmonary metastasectomy in soft-tissue sarcoma has also been associated with prolonged survival in appropriately selected patients with limited, resectable lung metastases. For patients with advanced ovarian cancer, interval cytoreductive surgery following treatment with neoadjuvant chemotherapy remains a standard approach. Patients undergoing interval cytoreduction have survival probabilities strongly associated with the degree of surgical cytolysis [44,45].

Although the evidence base is variable and generally limited, surgery has a role in the management of metastatic disease, where it is used appropriately based on tumour biology, extent of disease, response to systemic therapy and the individual patient's circumstances.

Surgery for Palliation in Advanced Metastatic Disease

Palliative surgery continues to play an important role in the management of patients with advanced metastatic disease, particularly when the tumor's progression may lead to significant morbidity, serious complications, or harm to the patient's function and well-being. Unlike resection with curative intent or with a premise of long-term survival, the purpose of palliative surgery is to alleviate symptoms, improve function, and maximize quality of life. A clear statement of goals and expectations is essential to justify such surgical endeavors in this context [3,46].

Palliative surgery is intended to improve the quality of life for patients with cancer who have life-limiting problems amenable to surgical intervention [3]. Many of the common indications for palliative surgery have been well established in the medical literature over the past century. These indications include the treatment of malignant bowel obstruction symptoms, management of pathological fractures due to metastatic disease, treatment of spinal cord compression symptoms, and control of tumor-related hemorrhage. The majority of indications for surgical intervention for malignant bowel obstruction are related to gastrointestinal and gynecological malignancies. Symptomatic patients with unresectable tumors who experience intractable pain, nausea and vomiting, and/or bowel obstruction may benefit from surgical bypass, creation of a stoma, or bowel resection to relieve these problematic symptoms. Pathological fractures due to metastatic disease of bone can result in severe, unacceptable pain and significant physical disability. Orthopedic stabilization and fixation with or without resection of involved bone can significantly reduce both pain and disability, allow continuation of effective chemotherapy, and dramatically improve physical function. Spinal cord compression is considered a true oncologic emergency. Patients who present with this medical condition require immediate surgical decompression. The majority of patients are also treated with radiation therapy and, in many cases, the result is return to presymptom neurologic function or better. Patients with life-threatening bleeding from gastrointestinal tumors and malignancies of the gynecologic organs may require surgical intervention to control bleeding when conservative measures fail [3,46].

The success of surgical palliation is measured by more than just survival. Most important is symptom relief, physical function, and patient-rated quality of life. For many patients, including some for whom surgical treatment was not considered possible initially, such benefits can be substantial and sometimes even lasting. For other patients, however, benefits may be minimal despite considerable morbidity from the surgery. Thus, the basis for advising patients that surgical palliation is a reasonable option rests with appropriate selection of candidates for such treatment. Whether a patient is able to return to full function within months, and whether his or her performance status places him or her at very high risk of serious operative morbidity or death, are critical factors in such decision making. Patients with very short life expectancy or reduced functional reserves are unlikely to benefit greatly from such an approach [3,46].

From an ethical perspective, the surgeon should attempt to weigh the potential benefit of any surgical intervention against the burden of that treatment. This means guarding against both futile treatment and overly burdensome interventions that may only serve to prolong uncomfortable dying rather than increase the patient's quality of life. As such, shared decision-making, honest and open communication, and the early integration of specialists in palliative care must become integral components of the surgical decision-making process and ensure that any treatment offered is one that is consistent with the patient's values, preferences, and overall goals [3,10,46].

Minimally invasive treatment and non surgical alternatives are increasingly taken into account in the palliative care and management of patients with malignancy. Endoscopic stenting, radiotherapy, embolisation, and image guided ablation all play a major role in the palliation of symptoms with significant reduction in morbidity. As part of a holistic, multidisciplinary approach these alternatives should be considered whenever appropriate [47,48].

Integration with Systemic and Local Therapies

Metastatic disease surgery is rarely undertaken in isolation and is usually part of a multimodal approach. Good coordination with systemic therapy and other local treatments is critical to improve survival outcomes. Decisions regarding the timing and combination of treatments must be highly individualized and made after thorough multidisciplinary discussion and consideration [17,42,49].

Surgery and Chemotherapy

Chemotherapy remains the mainstay of treatment for many patients with metastatic cancer. The impact of chemotherapy on the potential for surgical treatment of metastatic disease is an important consideration. Use of neoadjuvant chemotherapy can help predict tumor behavior, result in tumor downstaging, and identify the subset of patients with chemosensitive and less aggressive disease who are most likely to benefit from metastasectomy or cytoreductive surgery. Radiologic evidence of tumor response or stable disease during therapy serves as a useful surrogate marker for less aggressive disease [17,42,49].

The goal of adjuvant chemotherapy is the eradication of residual occult tumour left after surgery and the subsequent prevention of local recurrence. The often-subtle gains in therapy outcomes for patients with cancer must be balanced against the patient's recovery from major surgery and the additional toxic effects of chemotherapy. Good communication and cooperation between surgeons and oncologists are important to prevent unnecessary delays before beginning systemic therapy that could be dangerous for tumour control [33,36,45].

Surgery and Targeted Therapy

The integration of targeted therapies has added significant layers of complexity to the timing and appropriate role of surgical therapy in affected patients. In many instances, targeted therapies can induce marked shrinkage or prolonged stabilization of tumors, potentially offering new opportunities for the advantageous application of surgical techniques in patients who otherwise might not have benefitted from surgery. Targeted therapy is often utilized as initial therapy to select patients who sustain a durable response to therapy; subsequent surgical therapy is then proposed as a form of consolidative treatment to eliminate residual tumor [17,36,45].

The perioperative period is a time when the management of targeted therapy must be meticulously planned. Some targeted agents are known to interfere with wound healing, increase surgical bleeding, or have cardiovascular side effects. Decisions regarding the preoperative discontinuation and postoperative resumption of these agents, and the optimal interval between these events, are increasingly being investigated in the clinical literature [50].

Surgery and Immunotherapy

Recent advancements in immunotherapy have led to significant clinical improvements in several metastatic cancers, and interest in how immunotherapy can be combined with surgery to maximize clinical benefit has been reignited. Resection of tumor can reduce immunosuppression, decrease tumor antigen load, and potentially enhance the immune response. However, surgery is also known to cause transient physiological stress-induced immunosuppression, and careful consideration must be given to the timing of cancer resection in relation to treatment with immune checkpoint inhibitors and other immunotherapies [51].

While evidence supports a role for surgery in managing oligoprogressive disease to allow continued benefits of an effective systemic immunotherapy, the broader immunologic consequence of removing a tumor is not well defined and data are primarily of low-quality level.

Surgery versus Non-Surgical Local Therapies

In addition to medical therapies, non-surgical local therapies such as stereotactic body radiotherapy (SBRT) and other image-guided ablation techniques (radiofrequency ablation, microwave ablation, cryoablation, etc.) offer an alternative to surgical therapy for localized tumors. Excellent local tumor control can be achieved with these modalities and with decreased morbidity particularly for the patient who is a marginal or poor surgical candidate. An informed decision regarding the choice of surgical versus nonsurgical local therapies requires consideration of factors that characterize the tumor, the patient's comorbidities and performance status, the institutional expertise available, and a shared decision-making discussion amongst the members of the multidisciplinary team [33,42,52]

Risks, Limitations, and Controversies

While the role of surgery in metastatic disease has been expanding in recent years, important limitations and unresolved issues exist. The performance of major surgery in patients with advanced cancer is inherently associated with considerable risks of morbidity and mortality, and is

often complicated by comorbidities, frailty, malnutrition, previous chemotherapy and multiple lines of prior therapy [53,54]. Patients undergoing surgery for metastatic disease frequently suffer a significant decrease in quality of life and prolonged hospitalization. Moreover, the potential for serious postoperative complications can preclude further effective cancer therapy [55]. A careful consideration of whether or not surgical therapy will result in a positive net benefit for an individual patient is indicated [10].

A major concern in this context is that surgical therapy can potentially interfere with or delay administration of indicated systemic therapy. In many cases of metastatic disease, it is systemic therapy that constitutes the primary treatment modality expected to control the disease. Delay to or perturbation of scheduled systemic therapy, whether due to prolonged recovery from surgical therapy or from unforeseen surgical complications, can result in inordinate treatment gaps that may allow for cancer progression negating any potential benefit from resection or debulking surgery. The risk is particularly concerning for tumors with aggressive biology and in patients for whom the window to effective systemic therapy is narrow [56,57].

The available evidence often has to contend with marked selection bias. The majority of studies in support of metastasectomy and other surgical therapies for metastatic disease are based on retrospective cohort studies and single-institution series. The patients selected for surgical therapy in these reports are typically individuals with "good" patient characteristics, for example a low tumour burden, good performance status and a slowly progressing tumour [28,29,32]. Each of these characteristics are independent prognostic indicators for improved survival. Thus, it can be challenging to separate the effect of surgical therapy from the inherently favourable prognosis of the selected patients [58,59].

High-quality randomized controlled trials in Surgical Oncology are still lacking. Randomization is often precluded by ethical, logistical or practical considerations, and as such, much of the evidence base derives from observational data. On the rare occasions where well-designed randomised trials have addressed surgical questions in oncology, they have frequently challenged prevailing paradigms regarding the role of surgery in cancer treatment. It therefore is essential to be cautious in generalizing evidence from some tumor and patient populations to others [60].

A recurring theme across metastatic surgical oncology is the discrepancy between observational and randomized evidence. Several surgical strategies—including pulmonary metastasectomy for colorectal cancer, surgery of the primary tumor in metastatic breast cancer, and cytoreductive nephrectomy in metastatic renal cell carcinoma—were initially supported by retrospective studies demonstrating favorable survival outcomes. However, subsequent randomized trials frequently reported smaller benefits than anticipated, failed to confirm survival advantages, or demonstrated that benefit was restricted to highly selected patient populations. These findings underscore the importance of interpreting observational data cautiously and recognizing that favorable surgical outcomes may partly reflect underlying patient selection rather than treatment effect alone. As systemic therapies continue to evolve and improve, indications for surgery must be continually reassessed through prospective trials and multidisciplinary evaluation [37–41].

In addition to the risk of inadequate treatment and lesser quality of end-of-life care stated above, there is also a persistent risk of over-treatment of patients with life-limiting cancer and the associated risk of creating false hope for patients and families [61]. In order to avoid these harms, there is a need for uninhibited, honest discussion with patients and families, for treatment goals to be aligned with the patient's and family's values and priorities, and for thorough multidisciplinary evaluation and decision-making. Ultimately, the goal should be to choose treatments that are likely to offer benefit, as opposed to merely prolonging suffering [33].

Ethical and Shared Decision-Making Considerations

Decisions to justify surgery in metastatic disease must be made ethically with any potential benefit carefully weighed against substantial risks [10,62]. Regardless of the personal inclination of the surgeon, important decisions about surgery for metastatic disease should be governed by patient centered principles that match treatment choices with patient values, preferences, and goals of cancer care. Each patient would assign different weights to different objectives (e.g. survival, relief of symptoms, independence, quality of life), and decisions about whether or not to proceed with surgical therapy should reflect these goals. To be truly patient-centered, surgeons must be willing to refrain from offering surgery when the chances of achieving patients' objectives are slim, but to pursue aggressive surgical therapies when the benefits of doing so could significantly fulfill patient objectives [63].

Obtaining informed consent for proposed surgical treatment for metastatic cancer can be

particularly difficult and requires thoughtful discussion with patients and families. Importantly, patients and their relatives need to be adequately informed as to the precise objectives of proposed surgery whether these be curative, life-extending or palliative. An honest discussion of the expected benefits and potential risks versus benefits, as well as the uncertain outcomes, is critical. Furthermore, when surgical benefits are likely to be small, a thorough discussion of alternative non-surgical management strategies and the ambiguous prognosis are crucial to avoid raising false hope and to facilitate truly informed patient and family decisions [64].

When confronting the limitations of currently available oncologic therapies, one must consider not only the potential futility of continuing aggressive management for patient-specific indications, but also the broader implications of expending resources on major surgical operations in patients with advanced metastatic disease. Access to specialized teams, operating facilities and postoperative support can be very costly and is not equal across all oncologic centers and patient populations. Hence, the need for informed and responsible use of health care resources. This thoughtful allocation is fundamental to promoting health equity within oncology. Decisions therefore must be made with a keen sense of indications and expectations for benefit, rather than with a view to the capabilities of a multidisciplinary center [65,66].

Early and continuing involvement of palliative care specialists is an ethical imperative in the management of cancer patients. They bring a unique perspective and expertise to the team in the areas of symptom management, having difficult conversations, and clarifying goals of care. Their involvement ensures that any surgical intervention that is undertaken is consistent with the patient's overall goals and values, and that the treatment be as fully informed and holistic as possible. This is not a transition point from curative-intent treatment to palliative care, but rather a continuation of care that is more thoughtful, more compassionate, and more patient-centered as the disease trajectory continues [3,46].

Multidisciplinary Decision-Making

Decisions about surgery for patients with metastatic cancer involve multidisciplinary consideration of evidence regarding potential benefit against risk for patients with metastatic disease. These complex decisions cannot be made by one specialist in isolation. Multidisciplinary tumor boards provide an organized forum in which all relevant specialists and information can be gathered and individual treatment decisions developed in a consensus-driven fashion [33,67].

The input of surgeons is crucial in determining technical resectability and estimating surgery related risks and postoperative results. They define the boundaries of what can be achieved surgically in terms of complete metastasectomy, long term local control or even effective symptom relief. They also provide invaluable opinion regarding whether less invasive surgical approaches or alternative non surgical treatments may be indicated [68,69].

The medical oncologist has valuable insight into the tumour biology and the range of possible medical therapies that may be applicable. They can judge whether tumour control is likely with medical therapy or not, and if not, whether surgery would be likely to add additional benefit. They play a critical role in determining the timing of surgical intervention in relation to medical therapy [70].

Radiation oncologists possess considerable experience with non-surgical local therapies and can offer advice on the use of conventional radiotherapy, stereotactic body radiotherapy and other definitive ablative approaches which have been shown to achieve excellent local control with reasonable morbidity in selected patients. As a result, surgery is not always automatically chosen as the first line of treatment and must be weighed against alternative options [71].

Palliative care specialists can inform decisions about the likely burden of symptoms and what matters most to patients with respect to quality of life and their values and goals. Their opinions can help to steer other interventions that are unlikely to improve quality of life and focus on person-centered outcomes [3,46,72].

The bottom line is that with optimal multidisciplinary collaboration the treatment plan is developed with consideration of the biological behavior of the cancer, the patient's performance status and preferences, and all of the relevant therapeutic options. This is the key to ethical, evidence-based and patient-centered decision-making for surgical treatment of metastatic cancer [29,32,63]. Figure 3 shows the members of a multidisciplinary surgical oncology team.

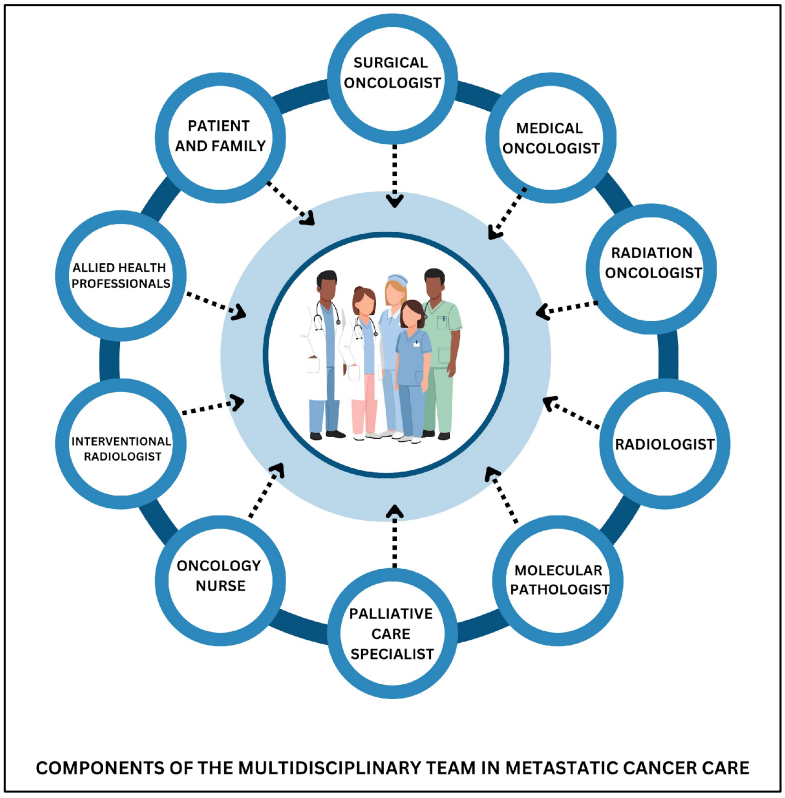

Figure 3: Multidisciplinary Team Approach to Decision-Making in Metastatic Cancer

Evolving Evidence and Future Perspectives

The future role for surgery in managing metastatic disease will depend on our ability to better identify patients for whom surgical therapy will be of most benefit. Developing better biomarkers to predict benefit of surgery for metastatic disease beyond factors such as burden of disease and performance status is a high priority. Measures such as levels of circulating tumor DNA, high tumor mutational burden, immune gene signatures, and markers of minimal residual disease are being explored as tools to improve candidate selection for potentially curative surgery as well as for monitoring response to therapy [73,74]. Figure 4 shows future directions in Metastatic surgery.

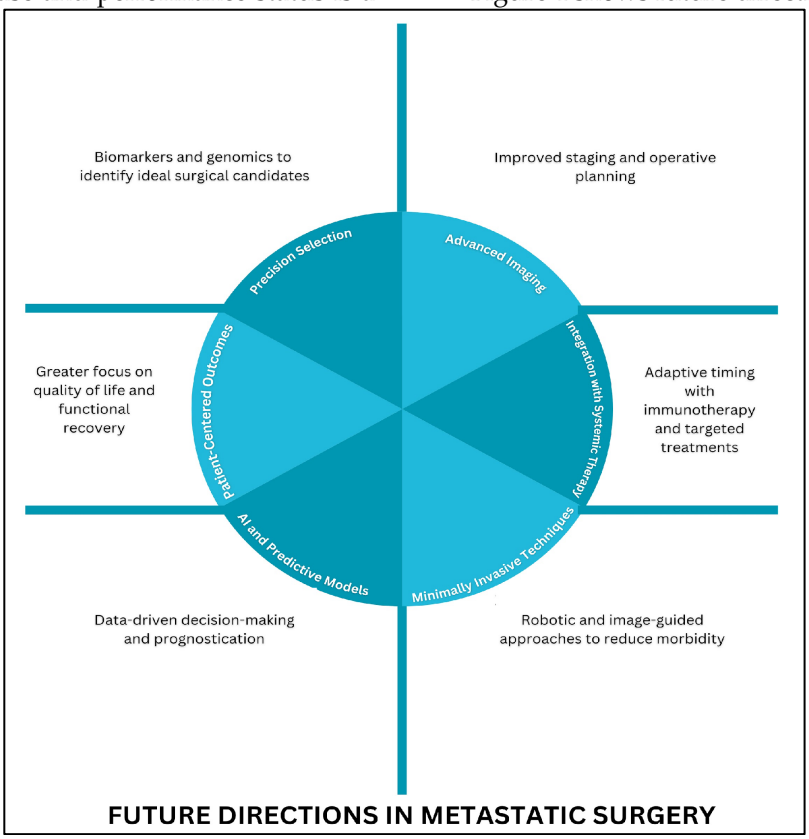

Figure 4: Emerging Trends in Surgical Management of Metastatic Disease

Advances in the fields of genomics and the comprehensive molecular characterization of metastatic cancer continue to elucidate key aspects of cancer biology. A more complete understanding of the mechanisms of disease, including patterns of clonal evolution, metastatic potential, and potential therapeutic targets, will enable clinicians to better distinguish indolent from aggressive disease. Future surgical indications for patients with widespread disease will be based not only on anatomic criteria regarding the potential for complete resection, but also on a prediction of durable cancer control following local therapy [75].

Prospective clinical trials of adequate design need to be undertaken to fill several remaining evidence gaps. High-quality research is required to better define the effect of surgery on survival and on quality of life for patients with different types of tumours and patterns of metastatic spread. In addition, studies are required to establish the best way to combine surgery with other forms of cancer therapy and the timing of surgery in relation to systemic therapy. Adaptive designs and biomarker-stratified trials may help overcome some of the difficulties faced in organising randomised trials in surgical oncology [60,76].

Emerging biomarker-driven strategies are likely to further refine patient selection for surgery in metastatic disease. Liquid biopsy technologies, including circulating tumor DNA (ctDNA) and circulating tumor cells, offer the potential to provide real-time insights into minimal residual disease, treatment response, and tumor evolution. As these technologies mature, ctDNA-guided decision-making may help identify patients most likely to benefit from metastasectomy or cytoreductive procedures while sparing others from unnecessary surgery in the presence of biologically aggressive disease. Early evidence suggests that postoperative ctDNA positivity is strongly associated with recurrence risk and may complement conventional radiographic assessment [77,78].

Another promising area is the integration of surgery with adaptive perioperative treatment strategies, particularly those involving immunotherapy. Neoadjuvant and perioperative immunotherapy may modify tumor biology, enhance systemic antitumor immune responses, and improve long-term disease control. Dynamic assessment using imaging, molecular biomarkers, and immune profiling may help guide the timing and extent of surgical intervention, allowing surgery to be tailored according to individual treatment response and disease biology [79,80].

Future prospective trials are increasingly expected to incorporate genomic alterations, molecular signatures, ctDNA status, and immune biomarkers into patient selection and stratification. Such approaches have the potential to move surgical decision-making beyond purely anatomical criteria and toward a more comprehensive assessment of tumor behavior. Collectively, these developments support a transition toward biologically informed precision surgery, in which operative decisions are guided not only by the extent of disease but also by the molecular and immunological characteristics of individual tumors [81].

Other emerging tools that may be valuable in future decisions regarding surgery for patients with metastatic disease include artificial intelligence and advanced predictive modeling. There is particular promise in the use of machine learning technologies to integrate clinical, radiologic, pathologic, and molecular data to enhance prognostication, predict which patients are most likely to benefit from an operative approach, and support truly personalized patient management [74].

Conclusion

Surgery has a more substantial role in the management of patients with metastatic disease than was once thought. For a select cohort of patients who have a limited burden of disease and who possess disease amenable to curative resection, surgery may confer a survival benefit. This role, however, must be judiciously integrated within a multimodal strategy of care and, certainly, within a thoroughly evaluated and multidisciplinary framework. The potential morbidity, the risk of overtreatment, and the chance of delaying or compromising effective systemic therapy must be rigorously weighed against potential benefits. As with all oncologic decisions, the process should be grounded and emphasize patient-centered, ethical-based determinations that correlate with the patient's overall goals and a satisfactory quality-of-life. As the molecular understanding of cancer progresses, as systemic therapies continue to improve, and as the ability to predict preoperative and postoperative clinical outcomes becomes more sophisticated, the skill to identify appropriate surgical candidates will improve.

Acknowledgements

Author Contributions: Conceptualization, P. J.; methodology, P. J., J. N.; validation, P. J., J. N.; writing – original draft preparation, P. J.; writing – review and editing, P. J., J. N.; Supervision, P. J. All authors have read and agreed to the published version of the manuscript.

Disclosures: No conflict of interest.

Funding: No funding was received.

Disclosure of AI Use: AI-assisted language editing tools were used solely to improve grammar, spelling, and clarity of the manuscript.

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