Future directions in the evaluation and management of newly diagnosed metastatic cancer

TITLE PAGE

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UNSTRUCTURED SUMMARY

There is much debate regarding optimal selection in patients with metastatic cancer who should undergo local treatment (surgery or radiation treatment) to the primary tumor and/or metastases. Additionally, the optimal treatment of newly diagnosed metastatic cancer is largely unclear. Current prognostication systems to best inform these clinical scenarios are limited, as all metastatic patients are grouped together as having Stage IV disease without further incorporation of patient and disease-specific covariates that significantly impact patient outcomes. Therefore, improving current prognostic scoring systems and incorporation of these covariates is essential to best individualize treatment for patients with metastatic cancer. In this narrative review article, we provide a detailed review of prognostication systems that can be used for both the site of metastasis and primary site to best tailor treatment in these patients. Additionally, we discuss the incorporation and ongoing developments in radiographic, genomic, and biostatistical techniques that can be used as prognostication tools.

INTRODUCTION

The optimal treatment for patients with metastases is unknown and largely depends on prognostication.[1] However, prognostication remains limited, as all of these patients are classified as Stage IV, which does not account for the heterogeneous nature of metastatic cancer **(Figure 1)**.[2] While guidelines vary by disease site, they typically involve the use of systemic therapy for all patients. While guidelines vary by disease site, they typically involve the use of systemic therapy for all patients. This approach is problematic, as patients who have a poor prognosis can be spared the morbidity of aggressive systemic therapy regimens. Conversely, patients with better prognoses can undergo therapy intensification, with local treatment (e.g., surgery or ablative radiotherapy) to the primary cancer or metastases with the dual goal of prolonging survival and maintaining quality of life[30,37]. However, it is presently unknown which of these two approaches is optimal[5,75]. Thus, comprehensive prognostication systems are needed to best identify patients who will benefit from aggressive local therapies. A timeline of the development of advancements in the management of metastatic cancer is presented in **Figure 2**.

While there are prognostication systems in multiple metastatic sites, they tend to be narrow in scope, as they do not simultaneously account for different disease sites and other patient specific covariates. Important clinical factors to consider when prognosticating patients with metastatic cancer by site of metastasis and site of primary cancer are presented in Table 1. While most cancer patients die due to metastatic disease, there are drastic survival differences among these patients, which are commonly driven by biological disease characteristics with associated response to systemic therapies, disease biology, performance status (PS), and competing risks of death. For instance, in patients with long estimated survival, clinicians may favor holding systemic therapy and employing local ablative treatments alone (Fig. 1)[3]. Conversely, patients with a poor prognosis

111 are more likely to be recommended for early palliative care[4]. Thus, improving the staging and
112 prognostication of metastatic patients is essential and will allow for improved treatment selection
113 and survivorship.

114 In the forthcoming sections, we conducted a narrative review of articles published in the
115 last 30 years. We review the pertinent literature and future directions for identifying and
116 developing ways to predict outcomes in metastatic cancer patients by site of involvement and by
117 primary cancer site. Additionally, we provide a detailed overview of current and evolving
118 strategies to prognosticate outcomes in metastatic cancer patients, such as genomics, nuclear
119 medicine, radiomics, exercise therapy, and biostatistics. This work will provide guidance in
120 optimizing care for metastatic patients and will provide further guidance on selecting patients
121 who are suitable candidates for local therapy (e.g, surgery, radiation therapy, cryoablation, and
122 high-intensity focused ultrasound) to the primary tumor and/or metastases, systemic therapy, and
123 early hospice.
124

PREDICTORS OF OUTCOMES FOR METASTASES BY SITE OF INVOLVEMENT

Prognostication in patients with metastatic cancer is largely dependent on the site of metastasis and the primary tumor. **Table 1** and **Figure 3** present factors shared by metastatic site and factors specific to the site of involvement. Based on the patient factors presented in each of the following sections, clinicians may consider different therapies, as shown in **Table 2**.

Lung

The lung is one of the most common sites for cancer metastases, with an incidence rate of 17.96 per 100,000.[5,6] Synchronous metastases most commonly arise from primary lung cancers, colorectal cancer (CRC), renal cell carcinoma (RCC), pancreatic cancer, and breast cancer.[6] Overall survival (OS) varies widely with 2-year rates of 42.1% and 4.1% for breast and pancreatic cancer metastases, respectively.[6] The burden of lung metastases is an important prognostic factor, with local ablative therapies for 1-3 metastases being associated with long term survival.[7] In 1997, a study from The International Registry of Lung Metastases of 5,206 patients who underwent a lung metastectomy across 18 international institutions identified multiple prognostic factors in these patients.[8] Important predictors of favorable outcomes were longer disease-free interval from primary disease, capacity to achieve complete resection, and fewer than 4 of pulmonary metastases, and germ cell histology.

Brain

Brain metastases are the most common intracranial neoplasm with an incidence rate of 7.3 per 100,000.[9] While lung cancer accounts for approximately 80% of brain metastases, breast cancer, melanoma of the skin, and RCC frequently metastasize to the brain. Survival in patients

with brain metastases at cancer diagnosis varies widely with median OS of 3-4 versus 20 months for gastrointestinal and hormone receptor positive/HER-2 positive breast cancers, respectively.[9] Predictors of tumor control, OS, and toxicity among patients with brain metastases at cancer diagnosis can be divided into patient characteristics, tumor attributes, and treatment parameters.[10] Many clinical neurological and overall prognostic tools have been validated including Karnofsky Performance Status (KPS) (with ≥ 70 favorable), Eastern Cooperative Group Oncology (ECOG) score (with 0-1 favorable), Recursive Partitioning Analysis (with stage I favorable), or Diagnosis-Specific Graded Prognostic Assessment (DS-GPA).[10,11] The most recent update of the DS-GPA includes patient-specific covariates for breast, non-small cell lung cancer (NSCLC) adenocarcinoma and non-adenocarcinoma, RCC, melanoma, and gastrointestinal cancers. These covariates include KPS, age, number of brain metastases, presence of extracranial disease, cancer subtype (breast cancer), presence of driver mutations (EGFR/ALK [lung], BRAF [melanoma]), and hemoglobin level (RCC).[10] The presence or absence of each of these covariates is assigned a score, with higher scores associated with an improved median OS. Additional factors, such as the presence of absence of neurologic symptoms, intracranial tumor volume, site of metastasis (e.g., brainstem versus non-eloquent cortex) and the presence of leptomeningeal disease, which is associated with a grim prognosis, are strongly prognostic.

Liver

Approximately 5% of cancer patients present with disease which has metastasized to the liver, with an incidence rate of 22.37 per 100,000 in 2015.[12] The most common tumor histologies to metastasize to the liver are lung, pancreas, colon, and rectum. Since approximately

50% of CRC patients develop liver metastases,[12] most of the data on prognostication derives from studies with CRC patients undergoing local treatment for hepatic metastases.

In a study of 484 CRC patients with liver metastases, KPS ≥ 80, smaller volumes of liver parenchyma involved by tumor (median OS 10.8 versus 4.5 months in ≤ 25% and > 75%, respectively), unilateral metastases, diameter of largest metastasis (8.3 versus 6.9 months in ≤ 5cm versus > 5cm, respectively), and absence of extrahepatic tumor were associated with better outcomes.[13] Furthermore, for patients with CRC undergoing hepatic resection, a preoperative carcinoembryonic antigen (CEA) level ≥ 50 ng/mL and the presence of a KRAS mutation has been associated with inferior survival.[13]

The use of stereotactic body radiation therapy (SBRT) in patients with 1-3 liver metastases is associated with local control (LC) rates exceeding 90%; additionally, lesions ≤ 3 cm in maximal diameter had a 2-year LC rate of 100%.[14] The median OS was 12 months versus 43 months for unfavorable (lung, ovary, and non-colorectal gastrointestinal primaries) and favorable (breast, colorectal, renal, carcinoid, and gastrointestinal stromal primaries) histologies, respectively. For breast cancer, estrogen-receptor negative disease, low albumin, and advanced age predict for poor survival.[15] Outcomes vary significantly by histology with the median OS in patients with liver metastases at time of cancer diagnosis ranging from 1-11 months for pancreas and rectal primaries, respectively.[12]

Bone

The bone is a common site for metastases, with an incidence rate of 18.8 per 100,000.[16] The most common cancers to metastasize to the bone are lung, prostate (men), breast (women), RCC, and pancreas.[16] Predictors of outcomes for patients with bone metastasis are determined by

patients' treatment and cancer origin. Chou et al. validated an accurate prognostic score including: ECOG performance status (PS) (0-1 favorable), primary cancer site (prostate, breast, nasopharynx favorable; other unfavorable), neutrophil-to-lymphocyte ratio (< 4 favorable), and platelet count (> 100 x 10^9/L favorable), for predicting mortality at 3, 6, and 12 months in patients diagnosed with solid cancers and bone marrow metastasis.[17]

Studies evaluating the predictors of outcomes following radiation therapy demonstrate that increasing target coverage decreases the risk of local failure post operatively.[18,19] The Mirels' Criteria utilizes four items and provides the risk of pathologic fracture following fixation for a long bone metastasis, where the lowest risk is observed in blastic lesions of the upper limb that involve < 1/3 of bone diameter and are associated with mild pain.[20] The Spinal Instability Neoplastic Score (SINS) is a similar tool that is used to determine the risk of instability in patients with spine lesions.[21] Studies evaluating post-surgical predictors of survival indicate that a white cell count > 11 x 10^9/L, sodium concentration <133 mEq/L, > 5 metastases, and primary tumor of gastrointestinal origin were significantly associated with reduced survival time.[22-24]

Oligometastases

Oligometastatic disease (OMD) represents an intermediate cancer state of limited spread, typically defined as 1 to 5 metastases on imaging.[25] Metachronous oligometastases, when metastases develop following a disease-free interval (DFI) ≥ 6 months after initial diagnosis, typically has an improved prognosis compared with synchronous (DFI ≤ 6 months) oligometastases.[26] Patients with a history of polymetastatic disease but response to systemic therapy to an induced oligometastasis generally have a worse prognosis than genuine oligometastatic disease. Several other prognostic factors have demonstrated an association with

decreased OS, including: nonadenocarcinoma histology, male gender, presence of intracranial metastases, synchronous (versus metachronous) oligometastases, initial TNM stage, increasing patient age and poorer PS, as well as increasing number of metastases (> 5), increasing total volume of metastases, and location of metastases.[27,28]

For these patients with OMD, the addition of metastasis-directed therapy (e.g., surgery or stereotactic radiotherapy) to standard-of-care systemic therapy is well-described in many retrospective reports to be associated with survival significantly longer than what would typically be observed in OMD treated with systemic therapy alone. A proposed framework for OMD patients most likely to benefit from metastasis-directed therapy can be divided into 1) patient factors: good PS (eg, ECOG 0-2), low disease burden (1-5 oligometastases), with effective systemic therapy options; 2) toxicity risk factors: small metastases, metastases in locations unlikely to cause major toxicity; and 3) timing factors: metachronous presentation and responding to systemic therapy.[29,30]

PREDICTORS OF OUTCOMES FOR METASTASES BY PRIMARY CANCER SITE

A major consideration when prognosticating outcomes in patients with metastatic cancer is the primary cancer site. **Table 1** and the forthcoming sections review prognostic factors associated with individual primary cancer sites.

Head and Neck

Selected patients with oligometastatic head and neck squamous cell carcinoma, especially HPV-associated oropharyngeal squamous cell carcinoma (HPV+ OPSCC), may benefit from local consolidative therapy.[31] A multi-institutional analysis of 82 patients with distant metastases

from HPV+ OPSCC showed that smoking history (never versus ever) and number of metastases (1 vs. 2-4 vs. ≥ 5) were associated with OS. Among 34 patients who developed metastases after primary surgical management of HPV+ OPSCC, 26 were oligometastatic (1-5 lesions) and had higher OS than those with polymetastases. Oligometastatic patients receiving definitive tumor-directed therapy following systemic therapy had improved OS compared to those undergoing systemic therapy alone. Among 40 patients with any oligometastatic HNSCC treated with radical local treatment of all tumor sites, factors associated with improved survival included better ECOG status, absence of bone and brain metastases, and lower total tumor volume, but not number of metastases or involved organ sites.[32]

Lung

Survival of patients with lung cancer metastases presenting with multiple metastases in one or more organs is particularly poor, with an estimated 2-year and 5-year overall survival of 10% and 0%, respectively.[33] The prognostic significance of a single-organ, solitary metastasis (M1b) was recognized in the American Joint Committee on Cancer (AJCC) 8th edition staging system update in 2017, which despite similar prognosis as intrathoracic metastatic disease to the contralateral lung (M1a), harbors distinctly improved survival when compared to the more common situation of polymetastatic lung cancer, usually in more than one organ, is classified as M1c, and staged as IVB.[33] In metastatic NSCLC, a spectrum of biologically distinct molecular phenotypes have recently been identified, each with unique natural histories and potential treatment options.[34] Treatment is largely guided by the presence of biomarkers, with actionable mutations necessitating the use of targeted therapies, and in the absence of a targetable

mutations, immunotherapy-based strategies informed by programmed death ligand-1 (PD-L1) biomarker expression levels.

Prostate

Historically, *de novo* metastatic hormone sensitive prostate cancer (mHSPC) has been defined on the basis of conventional imaging, general cross-sectional computed tomography and bone scintigraphy. Clinical risk stratification is typically based on definitions used to classify patients has having high-risk disease for the LATITUDE trial (any two of ≥ 3 bone metastases on bone scan, Gleason sum ≥ 8, and any visceral metastases)[35] or having a high extent of disease on the CHAARTED trial (defined as the presence of visceral metastases or ≥ 4 bone lesions with ≥ 1 beyond the vertebral bodies and pelvis vs. low volume).[35] These definitions have been validated as being prognostic, but their predictive value is unclear in the context of systemic therapy.[36,37] CHAARTED extent of disease, and more generally, the presence of ≤ 3 bony metastases and/or restriction to nonregional nodes, have been shown to be predictive for the benefit of prostate-directed radiotherapy.[38-40] Currently, no validated molecular biomarkers, prognostic or predictive, have been validated for mHSPC, but encouraging preliminary data suggest important roles for alterations in *AR*, *TP53*, cell cycle signaling, *MYC*, and *CTNNB1*, as well as for commercially-available genomic classifiers.[41] Notably, the advent of advanced molecular imaging will lead to an increased detection of metastatic disease at diagnosis, which may be of uncertain prognostic significance but will likely influence practice.[42]

Gastrointestinal

Patients with metastatic gastrointestinal cancer represent a heterogeneous group and outcomes vary widely based on the primary site. For patients with CRC, the presence of single organ versus multi-site metastases is an important predictor of outcomes, as reflected by the AJCC's creation of M1 subcategories in 2009.[43] The site, number, and size, of metastases, and pre-treatment CEA level are also associated with prognosis in these patients.[44,45] Local therapy for CRC with liver-only metastases can improve OS versus chemotherapy alone, and in some cases can be associated with long-term survival.[46] For patients with non-CRC primaries, a limited number of retrospective studies have shown that oligometastatic disease amenable to local therapies may also been associated with improved survival.[47,48] However, this data is limited and needs to be validated. Novel diagnostic imaging techniques may help to select patients with early metastatic disease to the liver to further investigate the role of local therapy in these patients.

Gynecologic

For metastatic cervical cancer, clinical factors including poor PS, multiple sites of metastases, extraosseous metastases, and short time-to-recurrence interval predict shorter survival time.[49] Older age, black race, and insurance status are also associated with prognosis.[49] Treatment factors also impact outcomes. The addition of pelvic radiotherapy to chemotherapy extends survival for selected metastatic cervical cancer patients, given the importance of pelvic tumor control. Platinum resistance predicts for poor outcomes for both cervical and ovarian cancers.[50] Women with higher levels of expression of excision repair cross-complement 1 (*ERCC1)*, a nucleotide excision repair gene implicated in tumor resistance to platinum

compounds, have been shown to have shorter OS after treatment with platinum-based chemotherapy for metastatic cervical cancer.[51] As therapeutic options expand, there is a need for biomarkers that can personalize therapy choices through dynamic insights into treatment response, such as miRNAs and circulating tumor cells or DNA, and predict response to immunotherapy through characterization of the tumor microenvironment.

Breast

Breast cancer represents the most common non-cutaneous cancer diagnosed in women in the United States. While outcomes have improved over the past few decades, women are at risk of developing distant metastases. Factors commonly associated with progression to distant metastases include young age, race, histologic grade, breast cancer subtype/receptor status, and stage at diagnosis.[52,53] When evaluating patients with metastatic breast cancer, predictors of outcomes include age, PS, breast cancer subtype/receptor status, bone only metastases, and number of metastases. Tumor genomic biomarkers are actively being investigated for prognostic or predictive value in patients with metastatic breast cancer and may have a role in personalizing therapy.[54-56] Combined with circulating biomarkers, genomic biomarkers have significant potential to guide therapeutic management of patients with metastatic breast cancer.

Sarcoma

Sarcomas are a relatively uncommon with 10,000-15,000 new cases each year in the United States. There is significant heterogeneity within the sarcoma disease site given the numerous histologies incorporated which range from soft tissue sarcomas to osteosarcomas to chondrosarcomas, each with their own treatment paradigms, patterns of failure, and prognostic

328 factors. Among patients with metastatic disease, treatment paradigms vary widely with curative
329 therapy attempted for those with limited metastatic disease (e.g., resection, ablative) as well as
330 those with certain histologies (e.g., Ewings sarcoma). Predictors of outcomes in patients with
331 sarcoma with metastatic disease include age, length of disease-free interval from initial
332 diagnosis, synchronous metastases at initial diagnosis, number of metastases, resection of
333 metastases, and presence/absence of local recurrence prior to development.[57]

PREDICTORS OF OUTCOMES IN METASTATIC PATIENTS

Tumor genomics and nuclear imaging have been shown to have prognostic value in metastatic cancer. Additionally, use of advanced biostatistical techniques and lifestyle modification can be used to further individualize treatment and improve outcomes. Different staging methodologies used in the metastatic setting are presented in **Table 3**.

Genomics

The past decade has seen an explosion of "liquid biopsy" assays that have made it feasible to detect circulating tumor-specific biomarkers in blood and other biofluids from cancer patients. These assays represent a myriad of technologies that measure circulating tumor cells (CTCs) or tumor-specific nucleic acids and have shown incredible promise in early detection of cancer, patient prognostication, post-treatment surveillance, treatment response monitoring, and evaluation for targetable driver mutations.[58,59] In patients with metastatic cancer of diverse histological types, both CTCs and circulating tumor DNA (ctDNA) fraction are correlated with disease burden and overall prognosis,[60,61] and therefore may have a role in guiding patient care decisions.

CTCs and ctDNA are increasingly being investigated in prospective clinical trials for circulating biomarker-based treatment personalization in patients with metastatic disease. Unfortunately, a randomized clinical trial of adaptive chemotherapy based on CTC kinetics in metastatic breast cancer failed to demonstrate improved patient outcomes – highlighting the need for more effective systemic therapies in patients with metastatic cancer who are not responding to current standards of care.[62] ctDNA kinetics are predictive of response to metastasis-directed therapy across many histological types of solid cancers. Additionally, ctDNA biomarkers in

metastatic disease have also shown promise in predicting the likelihood of benefit from immunotherapy and targeted therapy.[63]

Clearly, evidence supporting the clinical benefit of circulating biomarkers in patients with metastatic disease is likely to further expand in the coming years. However, an ongoing challenge will be the standardization of measurements across different assay platforms before they can be effectively incorporated into prognostic algorithms that are broadly applicable to metastatic cancer patients. Technological advances that enable tissue-type agnostic liquid biopsy assays, including implementation of deep learning computational methods to enhance signal-to-noise ratios, may have transformative potential in our ability to apply circulating biomarkers to improve prognostication of patients with metastatic cancer.[64]

Nuclear Medicine and Radiomics

Positron emission tomography (PET) molecular imaging enables a whole-body assessment of tumor burden, and can be performed with radiotracers targeting altered metabolic pathways in cancer cells (glucose with FDG, lipids with choline or acetate and proteins with fluciclovine or FDOPA)[65] or increased expression of cell surface proteins (prostate-specific membrane antigen (PSMA) with PSMA-11 or DCFPyL, somatostatine receptors with DOTATATE, estrogen receptors with fluoroestradiol). The tumor microenvironment can also be targeted by PET imaging radiotracers (osteoblasts with Na-F, cancer associated fibroblasts with Fibroblast-Activation-Protein Inhibitors (FAPI)) and may be used for cancer metastatic staging. PET-derived imaging information carries a strong prognostic value and is often critical for patient management.

There are a paucity randomized trials investigating the prognostic value of PET-based staging on patient outcomes. However, in multiple cancer types, PET has been shown to predict outcomes after specific therapies and is used as a standard-of-care staging tool to decide which therapy management algorithm to follow.[66,67]

In many cancer types, PET imaging is more sensitive than conventional imaging (ultrasound, CT, MRI, scintigraphic bone scan) and can upstage patients to M1 disease or detect additional metastatic sites. However, PET imaging is limited by the intrinsic sensitivity of PET scanner detectors. If the lesion is too small (e.g., microscopic disease) and/or does not have high increased metabolism and/or does not express the cell surface protein target in sufficient quantity and/or does not induce sufficient desmoplastic reaction, it can be not detected by PET.[68] Even if getting more and more sensitive thanks to large axial field-of-view and total body PET scanners, PET still shows the emerging and visible of part of the iceberg. There is an unmet need to differentiate patients for whom the visible lesions by PET represent the actual whole burden of the disease and the ones for whom there is more undetected disease. Radiomics, genomics and nomogram-based approaches may overcome this limitation by providing further refinement in sub-classifying patients with similar PET-pattern.

PET images can be further characterized by radiomic features to derive the imaging phenotype of the disease. These features can reflect, for instance, the heterogeneity of the signal within each lesion, and even more important in the context of metastatic disease, the heterogeneity between lesions, the total tumor burden, or the dissemination of the lesions. Some of these features, especially the total metabolic tumor volume and dissemination features, have already been demonstrated to bear significant and complementary prognostic values in both hematological malignancies and solid tumors, including when considering advanced stage

patients only.[69] With the fast-increasing development of radiomics, including deep radiomics based on the identification of features especially suited to prediction and prognostic tasks, it is expected that the radiomic phenotype will play a key role in prognostic and predictive models for guiding metastatic patient management. Beyond tumor foci, radiomic features pertaining to non-cancer tissues that define the metabolic and immune ecosystem in which the tumors develop should likely also be included in predictive models.

Biostatistics

To explore patients' heterogeneity for detecting potential predictors, the identification of phenotypical subgroups is of research interest and clinical importance. One commonly used approach for cross-sectional data is latent class analysis, a powerful statistical method to empirically investigate the structure of heterogeneity and identify underlying ("latent") subgroups with statistical associations among the observed variables as a manifestation.[70] Of note, this method has several advantages compared to regular clustering analysis (e.g., K-means), including rigorous statistical inference with efficient parameter estimates from the likelihood-based approach, flexibility to handle different types of variables, and the availability to assess misclassification when participants are assigned. In addition, if longitudinal data exist, Bayesian latent transition analysis can be performed to further investigate the stability of subtypes across time, with parameter estimation using the Markov Chain Monte Carlo technique.[71] If high-dimensional data are available, machine learning methods (e.g., random forest, extreme gradient boosting, support vector machine, neural networks) can be applied. Thereafter, the prediction models can be established to stratify patient subgroups, with predictive accuracy assessed by bootstrapping or cross-validation techniques. The STARS staging system, which was introduced

in 2021 utilized machine learning methods and data from over 500,000 patients to generate an internally and externally validated novel staging system incorporating all metastatic and primary disease sites.[1]

Patient Physical Activity

Hundreds of high quality randomized controlled trials document the robust benefits of aerobic and resistance exercise for symptom outcomes during and after cancer treatment, including improvements in fatigue, anxiety, depression, physical function, quality of life, sleep, and bone health.[72] The majority of clinical trials on this topic have focused on early stage patients and, to date, there are no published exercise oncology guidelines that specifically reference safety and efficacy in metastatic patients. However, review of the benefits among advanced cancer patients notes that metastatic patients can anticipate many of these same benefits from a program of three times weekly moderate intensity aerobic exercise for thirty minutes, along with twice weekly progressive resistance exercise. In a recently published review, trials that have included nearly 6,000 metastatic patients with a variety of tumor types confirm the safety and benefits of exercise for multiple outcomes, including physical function, fatigue, quality of life, and sleep issues.[73] The number of exercise oncology trials in metastatic patients has increased over the past decade, it might be expected that more definite recommendations regarding safety and benefits of exercise will be possible in the coming years. With regard to the effects of exercise on survival within metastatic patients, there are limited studies, but results are promising: greater physical activity has been observed to be associated with improved progression free survival in a cohort of 1218 metastatic colorectal cancer patients.[74]

CONCLUSION

Prognostication in patients with metastatic cancer is a multifactorial process. Disease outcomes are largely dependent on site of involvement, as well as molecular and genomic factors. The use of radiomics, computational biology, and lifestyle modifications can both aid in optimization of therapy and improvement in outcomes for these patients.

TABLES

Table 1: What data should clinicians collect about metastatic patients when making treatment decisions?

All Patients	- Driver mutations/systemic therapy options - Volume of disease, volume of each metastasis - Number of metastases in each site (e.g., 1, 2, 3, 4, 5+) - Location of "other" sites of metastases - Charleson-Deyo comorbidity score - ECOG/Karnofsky performance status - Patient age - Exercise/physical activity - Social history - T-stage / N-stage - Histology - Metachronous vs synchronous - Growth pace of metastases - Time of and adequacy of imaging acquired for staging - Ability to resect and/or ablate
Lung metastases	- Primary cancer site (e.g., breast [favorable] versus pancreas [unfavorable]) - Number of metastases (1-3/5 [favorable]) - Disease-free interval
Brain metastases	- Primary cancer site (e.g., NSCLC [favorable] versus gastrointestinal [unfavorable]) - Intracranial tumor volume - Extent of extracranial disease - Tumor location (e.g., brainstem versus non-eloquent cortex) - Presence of neurologic symptoms - Driver mutations - Leptomeningeal disease - RPA class - DS-GPA index

Liver metastases	- Primary cancer site (breast, colorectal, renal, carcinoid, GI stromal tumors [favorable] versus lung, ovary, non-colorectal GI [unfavorable])
	- Volume
	  - Unilateral (favorable) versus bilateral (unfavorable) involvement
	  - Lesion size (> 5 cm unfavorable)
	  - Presence or absence of extrahepatic tumor
	  - Percent of liver involved (> 75% [unfavorable]; < 25% [favorable])
	- ER positivity (if breast primary)
	- KRAS, CEA markers (if colorectal primary)

Bone metastases	- Primary cancer site (prostate, breast, nasopharynx [favorable] versus other [unfavorable]) - NLR (< 4 favorable) - Platelet count (> 100 x 10^9/L [favorable]) - Serum sodium (< 133 mEq/L [unfavorable]) - WBC count (> 11 x 10^9/L [unfavorable]) - SINS score (>11 [favorable]; <7 [unfavorable]) - Mirels Criteria (>11 [favorable]; <7 [unfavorable])

	- Extent
Oligometastases	- Disease-free interval - Prior response to systemic therapy - Disease burden - Nonadenocarcinoma histology (unfavorable) - Male gender (unfavorable) - Presence of intracranial metastases (unfavorable) - > 5 oligometastases (unfavorable)
Primary Site-Specific Factors	Prostate: PSA, Gleason score Breast: ER/PR, HER2, BRCA Lung: ALK, EGFR, ROS1, KRAS, PD-L1, MET, TRK Esophagus: HER2, PD-L1, CRS score Colorectal: MSI, MMR, BRAF, KRAS, CEA, ctDNA Melanoma: BRAF Pancreas: RAS, BRCA Head and Neck: HPV, EBV

Abbreviations: CEA: carcinoembryonic antigen; CRS: chemotherapy response score; ctDNA: circulating tumor deoxyribonucleic acid; DS-GPA: diagnosis specific graded prognostic assessment; EBV: Epstein-Barr virus; ECOG: Eastern Cooperative Oncology Group; ER: estrogen receptor; GI: gastrointestinal; HPV: human papillomavirus; MSI: microsatellite instability; NLR: neutrophil-to-lymphocyte ratio; NSCLC: non-small cell lung cancer; PR: progesterone receptor; PSA: prostate specific antigen; RPA: recursive partitioning analysis; SINS: spinal instability neoplastic score; WBC: white blood cell; WBRT: whole brain radiation therapy

Table 2: Selecting patients with metastatic cancer for aggressive local treatment, systemic therapy alone, or palliative care only

What type of patient is best for aggressive local therapy to the primary and metastases (e.g. stereotactic body radiation therapy, resection of primary)?
- Low volume of metastatic disease (e.g., 1-5 sites) - Ability to completely resect/ablate metastases - Oligoprogressive patients - Response to systemic agents (e.g., well controlled systemic disease with few sites of oligometastasis or oligoprogression) - Long interval to oligoprogression (e.g., > 6-12 months) - ECOG 0-2 performance status - ECOG 3-4 performance status not able to tolerate systemic therapy with good estimated survival and no (or few) competing risks of death
What type of patient should receive systemic therapy, without local aggressive therapy?
- High volume of metastatic disease (e.g., >5 sites) - Polyprogression / many sites of new disease, rapid timeline/"tip of the iceberg" presentation - Short time to progression (e.g., < 6-12 months) - ECOG 0-2 performance status (depending on systemic therapy options)
What type of patient should receive early hospice (without aggressive local and/or systemic therapies)?
- High volume of metastatic disease (e.g., >5 sites) - Polyprogression / many sites of new disease, rapid timeline/"tip of the iceberg" presentation - Short time to progression (e.g., < 6-12 months) - ECOG 3-4 performance status (depending on systemic therapy options)

Abbreviations: ECOG: Eastern Cooperative Oncology Group

Note: These are proposed patient groups requiring further validation

Table 3: Summary of staging tests currently available for metastatic disease, with pros and cons of each

Test	Pros	Cons
AJCC TNM	- Ease of use across disease sites - Disease sites allow for stratification by extent of metastatic disease (e.g., lung cancer – M1a vs. M1b vs. M1c)	- Does not take patient specific covariates into account, such as performance status, driver mutations and genomics
Nuclear Imaging	- Allows for whole body assessment of tumor burden - Different radiotracers targeting different molecular mechanisms can be utilized (e.g., FDG, DOTATATE, Fluciclovine, FAPI) - Highly prognostic	- High cost - Sensitivity limited by sensitivity of PET scanner detectors - Limited availability
Liquid Biopsy Assays (e.g., ctDNA and CTC)	- Correlation with disease burden and overall prognosis - Can be used to predict response to targeted and immunotherapeutic agents - Can be used to tailor systemic therapy	- High cost - Limited availability - Limited randomized data - Lack of standardization of measurements
STARS	- Incorporates all sites - Externally validated	- Lacks number of metastases, volume of metastases, most disease-site specific biomarkers/mutations

Abbreviations: AJCC: American Joint Committee on Cancer; FDG: fluorodeoxyglucose; FAPI: Fibroblast-Activation-Protein Inhibitor; PET: position emission tomography; TNM: tumor, lymph node, metastasis

FIGURE LEGENDS

Figure 1. The wide spectrum of metastatic cancer

Metastatic cancer occurs on a wide spectrum. Patients on the left are most favorable and are frequently treated with aggressive local therapies without systemic therapies, while patients on the right are the least favorable and are frequently enrolled in early hospice. However, most metastatic patients are managed with systemic therapy alone, which is often suboptimal.

Figure 2. Timeline of major developments in the treatment of metastatic disease

Major developments in the management of metastatic cancer over the past 80 years. Systemic therapies (red), local therapies (blue), genomics (green), radiology and nuclear medicine (black)

Figure 3. Predictors of outcomes in metastatic patients

Predictors of outcomes by site of metastasis (red), site of primary tumor (blue), and methods to further aid in prognostication using genomics, radiomics, and biostatistics (green)

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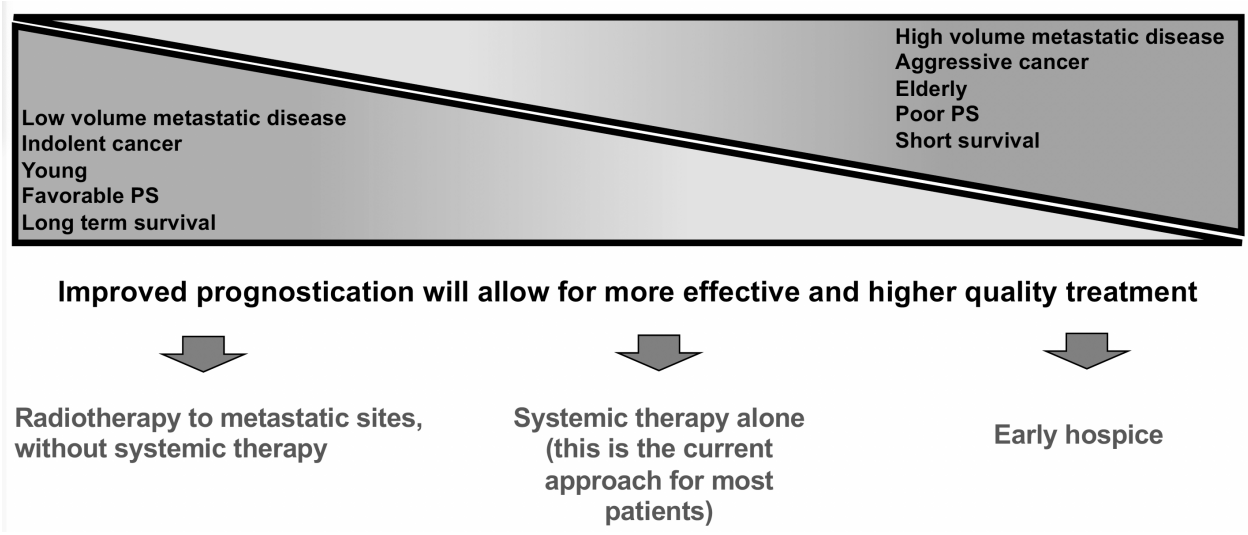
678 Figure 1



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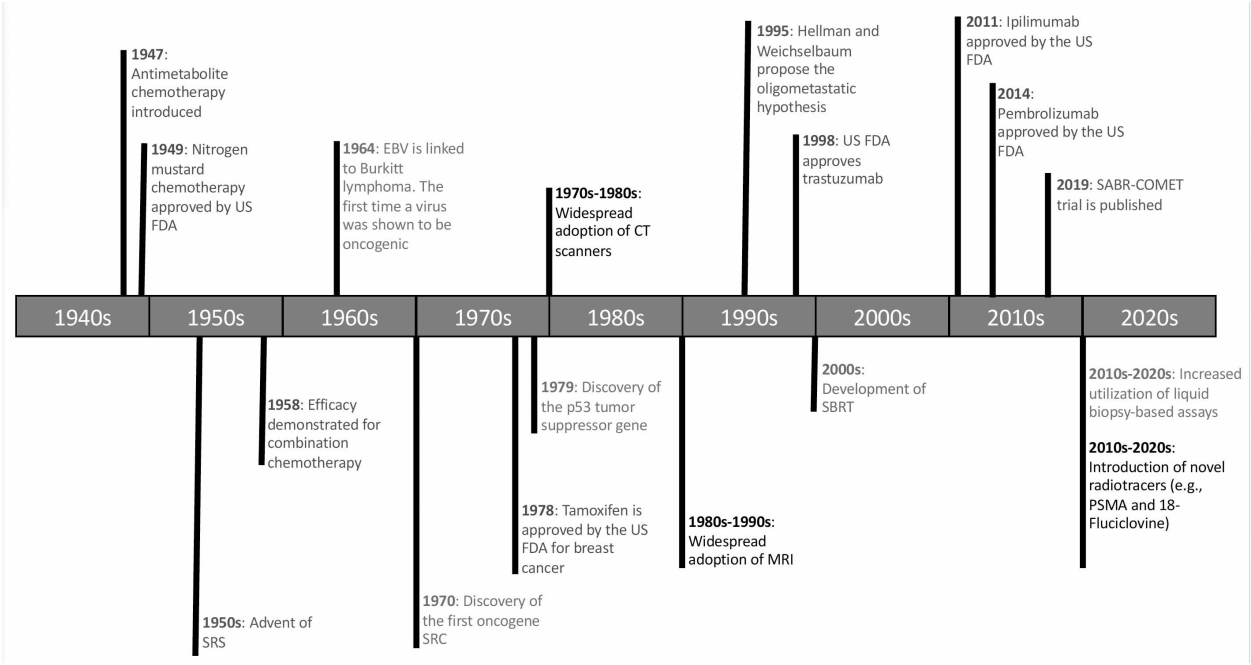
681 Figure 2



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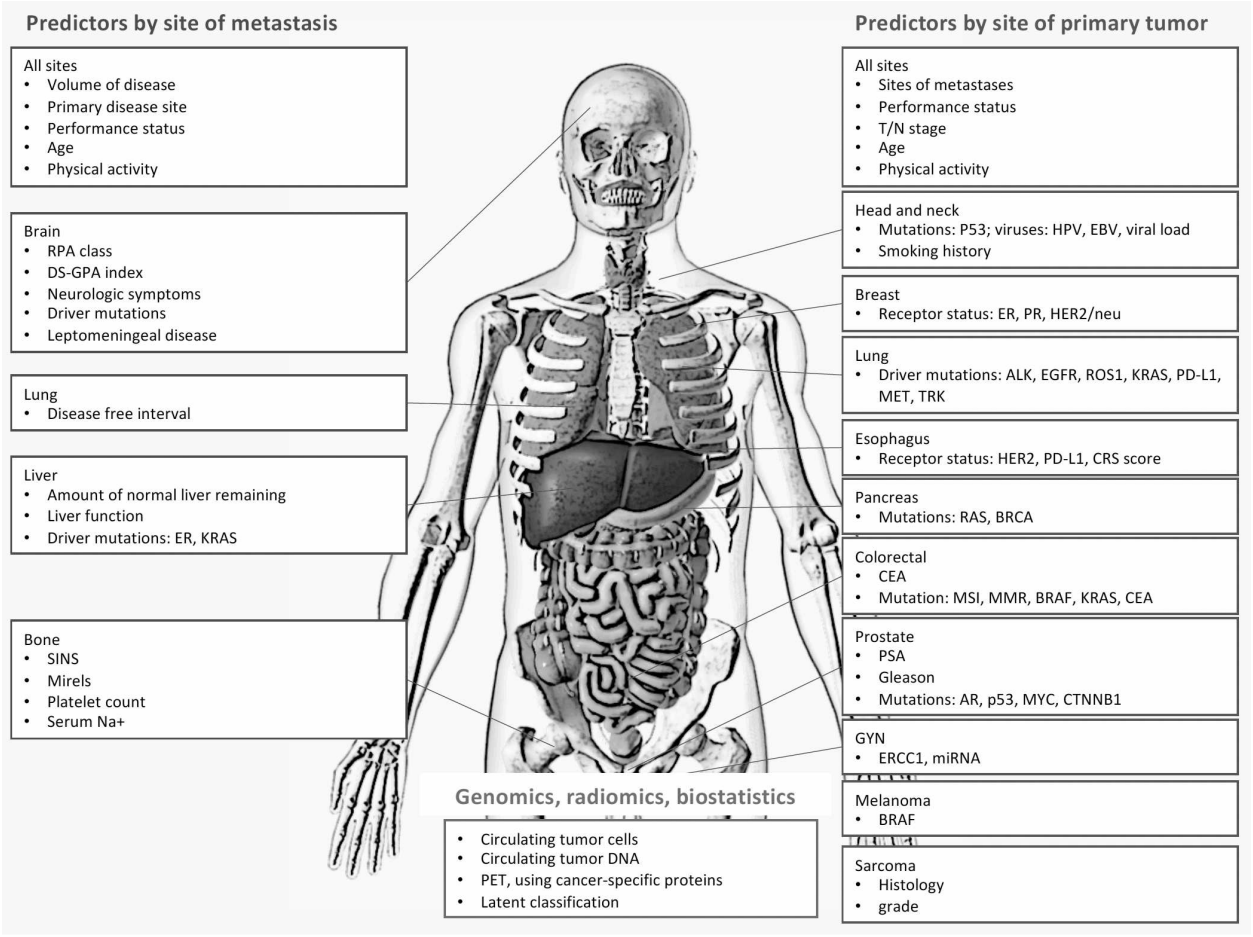

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