Imaging Oligometastatic Cancer

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Abstract

The term oligometastases is in common clinical use, but remains poorly defined. As novel treatment strategies widen the therapeutic window for patients defined as having oligometastatic cancer, improved biomarkers to reliably define patients who benefit from these treatments are needed.

Multimodal imaging should be optimized to comprehensively assess the metastatic sites, disease burden and response to neoadjuvant treatment in each disease setting. These features will likely remain important prognostic biomarkers, and are critical in planning multidisciplinary treatment. There are opportunities to extract additional phenotypic information from conventional imaging, while novel imaging techniques can also image specific aspects of tumour biology. Imaging can both characterise *and* localise the phenotypic heterogeneity of multiple tumour sites. Novel approaches to existing imaging datasets, and correlation with tumour biology, will be important in realizing the potential of imaging to guide treatment in the oligometastatic setting. This article discusses the current status and future directions of imaging in patients with extracranial oligometastases.

Introduction

The identification of 'oligometastases'[1] reflects a cohort of patients with metastatic cancer who can be treated with radical intent. Although Hellman and Weischelbaum first coined this terminology in 1995 to reflect metastatic disease limited in size, number and metastatic potential, pulmonary and hepatic resection for metastatic disease predates their description by over half a century.[2] It remains unclear whether oligometastases are a definable biological entity in the evolution of some tumours,[3] or simply a useful classification of patients with metastatic disease based on the opportunity for intervention with radical intent.[4] There is a paucity of randomized clinical trials, consequently observational evidence is cited for the clinical efficacy of intervention: 27-68% of patients with colorectal cancer (CRC) undergoing pulmonary[5] and 28-49% of patients undergoing hepatic[6] metastasectomy achieve 5-year survival, with some long-term survivors, which compares favourably with the wider cohort of patients with metastatic disease.

These retrospective studies have also provided data on prognostic features in patients having metastasectomy. There are patient factors, primary tumour features and measures of metastatic disease burden (size, number and distribution), which are reported to be predictive of overall survival (OS) in some settings.[e.g.5-8] This has informed the clinical definition of oligometastases and shaped clinical practice. More recently, the increased availability of therapeutic options and more aggressive clinical

practice in treating oligometastases mean that these conventional prognostic 'biomarkers' used to triage patients who might benefit from intervention, may be inappropriate to use in the changed clinical landscape.

The goal of imaging in patients with suspected oligometastatic cancer is, firstly, to provide a comprehensive account of all sites of disease, so local treatment can be planned and, secondly, to contribute to an overall assessment of likely subsequent disease behaviour, in combination with clinicopathological biomarkers, to justify a radical approach to metastatic disease. Conventional imaging, computed tomography (CT), multiparametric magnetic resonance imaging (MRI) and ^{18}F-fluorodexoyglucose-positron emission tomography (FDG-PET), plays a central role in assessing the metastatic disease burden in patients with suspected oligometastatic cancer, in treatment planning, in determining disease response, and as a prognostic indicator. Novel imaging methodologies, which can non-invasively characterise the intra- and inter-lesional heterogeneity of all tumours within a patient at multiple time points over the course of treatment,[9] may have further utility as prognostic and predictive biomarkers in this setting.

The aim of this article is to review current state-of-the-art imaging of extracranial oligometastases in patients with cancer. We discuss the clinical issues in assessing the disease burden and highlight the potential for developing imaging biomarkers for tumour characterisation and prognostication.

The therapeutic opportunity

There is growing academic interest in oligometastases (Figure 1), in parallel with an expansion in clinical intervention in this setting both in the UK and US: the hepatectomy rate in UK patients with colorectal liver metastases increased from 1.7% in 1998 to 3.8% in 2004, but with significant variation from region-to-region,[10] while US data shows increase in most common metastasectomy procedures across several cancer types.[11] While surgical metastasectomy remains the dominant treatment modality for patients considered oligometastatic, this has also coincided with greater acceptance and adoption of local ablative techniques. These techniques, particularly stereotactic radiotherapy (SBRT),[12] allow multiple sites to be treated, and are typically less morbid than surgical metastasectomy. Oncologists are now offering locally-directed therapy in most common tumour types and at the majority of disease sites.[13] There are numerous ongoing trials evaluating SBRT and radiotherapy for treating oligometastases.[14]

As these modalities have gained wider acceptance in clinical practice, advances in surgical practice have broadened the criteria for resectability,[15] and local ablative

techniques are now routinely considered as part of a multimodal treatment strategy, meaning more advanced disease can be treated. For patients with resectable metastases from CRC, more effective neoadjuvant chemotherapy has also improved the progression-free survival,[16] while 'conversion' chemotherapy can render patients with initially unresectable disease operable.[17] It is also recognized that patients with multi-organ metastatic disease can achieve long-term survival if treated aggressively,[18] providing clinical justification for combined treatment approaches. There has also been a fall in perioperative morbidity,[11] which may lower the threshold for considering metastasectomy.

Although the "therapeutic opportunity"[4] presented by limited metastatic disease is growing, the oligometastatic state remains undefined for the majority of cancers and, even for established settings, clinical practice continues to evolve. Labelling patients as oligometastatic provides an opportunity for aggressive radical treatment but, without level 1 evidence evidence for efficacy, this, may expose patients to futile therapies with their associated costs, morbidity and mortality, without clinical benefit. Existing prognostic biomarkers derived from retrospective series predate modern therapeutic options, and appear not to appropriately stratify patients for treatment.[19] In the setting of widening clinical opportunities for intervention, robust and consistent work-up is crucial, and developing novel prognostic biomarkers a priority.

Assessment of disease burden in oligometastatic cancer

Potentially oligometastatic parenchymal disease may be detected as part of initial staging; for example, 15-20% of patients with colorectal cancer have synchronous metastatic liver disease.[20,21] Metachronous oligometastases or oligorecurrence[2] may emerge during imaging surveillance or be detected following imaging performed in response to emerging clinical symptoms or rising serum biomarkers (e.g. carcinogen embryonic antigen, CEA). Oligoprogression[2] is the phenomenon of progression of a limited number of metastatic deposits, while other metastases are controlled by systemic therapy. These sub-classifications of oligometastatic disease have not been studied as different entities in the past and, from a practical perspective, the imaging considerations are similar.

One of the most critical functions of imaging a potentially oligometastatic patient considered for metastasis-directed therapy is verifying the true burden of metastatic disease. Contrast enhanced CT (ceCT), is generally used as the initial imaging modality for whole-body imaging,[22] due to its wide availability and relatively low cost. Following detection of metastatic disease, patients with suspected oligometastatic cancer may benefit from further tailored imaging to accurately define the metastatic burden. This facilitates careful planning of the therapeutic strategy.

Whole-body imaging investigations

Modified-protocol CT and dual-energy CT

Standard ceCT for staging or re-staging cancer includes thoracic imaging, and a portal venous phase CT of the abdomen and pelvis. For some cancers, the addition of an early phase acquisition to standard protocols can significantly improve detection of hypervascular metastases from primaries such as renal cell carcinoma (RCC) and neuroendocrine tumours (NET).[23]

Similarly, dual-energy CT (deCT) has the potential to improve image contrast for parenchymal metastases, particularly in the liver, pancreas and kidneys. Again, potential advantages may be observed for hypervascular lesions, or for hypovascular lesions in a background fatty liver.[24] Currently there is insufficient evidence for the advantage of deCT for lesion detection, but clinical evidence for efficacy is likely to emerge as more clinical systems offer this facility and comparative data are routinely acquired.

Whole-Body MRI

Whole-body MRI (WB-MRI) is an emerging imaging technique that has been tested in several disease settings, including breast and colorectal cancer, with reported per-patient sensitivities of over 90%, comparing favourably with ^{18}F-FDG-PET/CT (FDG-PET/CT).[25] There are ongoing clinical trials assessing its diagnostic role and efficacy, typically compared against FDG-PET/CT.[1] The techniques are still evolving, and require optimization for each malignancy, taking into account likely metastatic sites, practicality and general applicability.

FDG-PET

FDG-PET has been widely adopted in staging patients with oligometastases planned for metastasectomy, typically in combination with attenuation correction CT (FDG-PET/CT). It detects additional disease with a resultant change in management in nearly a quarter of patients in some populations.[26] This has clinical utility: for example, the use of FDG-PET/CT improves patient selection for hepatic metastasectomy, with improved survival compared to historical data in patients not investigated by FDG-PET or FDG-PET/CT(22),[27] and fewer futile laparotomies.[28] The Royal College of Radiologists recommends FDG-PET/CT for staging patients with metastatic disease from colorectal cancer, sarcoma and melanoma prior to radical therapy,[29] and there is consensus that it is required for staging patients prior to SBRT.[13]

[1] HTA - 10/68/01: Comprehensive staging of newly diagnosed lung and colorectal cancer: Prospective multicentre comparison of whole body Magnetic Resonance Imaging with standard diagnostic imaging pathways (http://www.nets.nihr.ac.uk/projects/hta/106801)

For patients with hepatic metastases, for the most part, the benefit of FDG-PET/CT is detecting previously unreported extra-hepatic disease, rather than improved hepatic disease detection. In colorectal cancer, the per-patient sensitivity of FDG-PET/CT is at least as good as MRI, but the per-lesion sensitivity is inferior.[26] Disease detection in the liver is hampered by the high background hepatic signal, which may mask small volume disease, and the anatomical localisation is inferior to MRI. The use of novel reconstruction algorithms in PET/CT improves the signal-to-noise and signal-to-background ratio,[30] and may improve the detection of small volume hepatic metastatic disease with FDG-PET/CT.

Clinical systems that combine PET with MRI (PET/MRI) have been available since 2010, although uptake has been limited. For metastatic disease, studies have predominantly reported a similar overall diagnostic performance of FDG-PET/MRI to FDG-PET/CT, although there may be advantages for certain disease sites, such as bone metastases.[31] There may be workflow advantages for PET/MRI where both PET and MRI are required for clinical assessment of oligometastases, such as in patients with liver metastases, or to allow simultaneous multiparametric phenotypic assessment.

Disease specific imaging

More recently, tracers other than FDG have been shown to improve disease detection in the context of potential oligometastatic disease in specific diseases. For instance, sodium fluoride is significantly more sensitive in the detection of bone metastases in breast[32] and prostate[33] cancer than conventional technetium bone scanning. Fluoroethyl choline and fluoromethyl choline have also been shown to be superior in the detection of prostate cancer metastases in comparison to FDG-PET/CT, and are now used routinely for the detection of radically treatable local or oligometastatic relapse in patients with biochemical relapse.[34] Other tracers, such as the synthetic amino acid tracer anti1- amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid (FACBC), may further improve sensitivity for locally treatable oligometastatic prostate cancer relapse, and are under ongoing investigation.[35]

Liver-specific imaging

The liver is a common site of parenchymal metastases from solid organ tumours, and the prevalent site for gastrointestinal malignancies; as many as 50% of patients with colorectal cancer develop liver metastases during the course of their disease.[20,21] Patients with limited metastatic liver disease may be considered for locally-directed intervention with radical intent. In these patients, accurate identification of each site of liver involvement is critical, particularly in relation to the surgical anatomy, to allow treatment planning and patient counseling.

The sensitivity of ceCT for colorectal metastatic disease in the liver is approximately 85% on a per-patient basis, falling to 74% on a per-lesion basis.[36] This is inadequate in the radical setting and therefore liver-specific imaging is normally considered. Conventional ultrasound has a modest sensitivity for hepatic metastases,[37] and is therefore not advocated as an adjunct to CT staging. Although contrast-enhanced ultrasound of the liver is recommended in some settings, there are no significant gains in per-patient or per-lesion sensitivity over ceCT,[38,39] and therefore it is not routine in this setting. Multiparametric magnetic resonance imaging (MRI), incorporating multiphase gadolinium-enhanced and diffusion weighted sequences, has a per-lesion sensitivity of over 80%,[36,38] with further gains reported through the use of liver-specific contrast agents, particularly for small lesions.[37,40] Multiparametric MRI has become the modality of choice for liver-specific imaging in patients with metastatic disease and should be considered mandatory for all patients where liver-directed intervention for metastatic disease is considered.

Improved diagnostic imaging and patient selection

Advances in imaging technique have produced improvements in the sensitivity of diagnostic tests. As a result, we can now detect disease that would have previously remained occult. Indeed, given the incidence of relapse in the first 3 months after hepatic resection,[41] there is likely to be further clinically-relevant occult metastatic disease. It is uncertain if this additional disease confers a negative impact on survival; residual small volume disease may be controlled by effective systemic chemotherapy or host immunity. However, using FDG-PET to detect occult disease has improved outcomes compared with historical cohorts in patients with colorectal cancer, suggesting PET-detected disease is prognostically relevant.[28] More sensitive staging may prevent futile intervention.

Conversely, we should not to be overzealous in applying imaging biomarkers that were developed in historical cohorts using less advanced imaging techniques, to patients staged using modern imaging strategies. More sensitive imaging strategies risk patients being incorrectly classified as ineligible for potentially curative treatment if this is based on historic precedents, as smaller volume disease will now be detected. Although, for example, four or more liver metastases was historically viewed as a relative contraindication to surgery, there are modern cohorts with acceptable survival despite more than three metastases,[42] likely due to more sensitive imaging and improved chemotherapy. Finally, we should recognize that adhering to established selection criteria, while adopting more sensitive imaging strategies, would create a stage migration bias[43] in more recent or future oligometastatic cohorts, if higher risk oligometastatic patients are re-classified as polymetastatic.

Imaging as a biomarker of oligometastatic cancer

A biomarker is a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".[44] In the era of precision cancer therapy, prognostic biomarkers can help select patients who benefit from radical treatment. The outcomes for patients undergoing radical treatment for oligometastases, even in established settings where there is a wealth of retrospective data, are highly variable, suggesting a failure of prognostic biomarkers to adequately guide treatment.[41,45]

Imaging biomarkers are already widely used in cancer. The TNM staging system and response to treatment are both prognostic biomarkers across a broad range of cancers. Imaging can assess spatially disparate tumours at multiple time points and may, therefore, have particular utility as a biomarker in the metastatic setting, where tumour-derived biomarkers (biopsy or serum) may be unable to assess multisite disease, or fail to preserve spatial information. Inter- and intra-lesional heterogeneity, an important feature of tumour development,[46] can only be assessed by techniques that can preserve this information. Alternative biomarkers in development, particularly circulating biomarkers, will allow temporal changes to be assessed, but determining their site of origin is challenging, and may not be possible where there are multiple heterogeneous metastatic sites within the same organ.[47] There may be a future synergy between novel imaging and circulating biomarkers.[9]

Conventional imaging biomarkers in oligometastatic cancer

Imaging plays a pivotal role in describing the total metastatic disease burden in patients with oligometastatic disease. As discussed above, the staging strategy should be tailored to the primary tumour and metastatic site(s). A higher pre-operative disease burden is associated with worse outcome: the number, size and distribution of metastases have been found to be prognostically relevant when considering, for instance, patients with colorectal cancer undergoing lung or liver metastasectomy (Table 1).[5,6,45] For other local ablative treatments, there is now emerging evidence that similar markers of disease burden are prognostically relevant.[7,8] Treatment decisions are informed by these criteria; patients with poor prognostic factors may receive neoadjuvant chemotherapy prior to resection, or may be considered unsuitable for radical treatment.

Table 1: Occurrence of prognostic imaging biomarkers for resected colorectal liver metastases (adapted from the review by Spelt and colleagues, 2012)[6]

Legend: n = number of patients in analysis; number = number of liver metastases; bilobar = metastases in both the left and right lobe of the liver; size = size of the largest metastasis; EHD = extrahepatic disease; + = factor identified as predictive; - = factor identified as not predictive; blank field = factor not analysed.

Study Author	Nordlinger	Rees	Fong	Malik	Zakaria	Yamaguchi	Minagawa	Iwatsuki	Tan	Schindl	Konopke	Tanaka	Lise	Ueno	Nagashima
n	1568	1005	1001	687	662	380	369	305	285	269	201	149	135	85	81
Publication Year	1996	2008	1999	2007	2007	2008	2007	1999	2008	2005	2009	2004	2001	2000	2006
Number	+	+	+	+	-	+	+	+	-	+	+	-	+	+	+
Size	+	+	+	-	-	+	-	+	-	-	-	-	-	-	+
Bilobar	-	-	-	-	-	-	-	+	-	-	-	+	-	-	-
EHD		+	+			+	-	+				-			+

However, prognostic scores based on disease burden biomarkers were not developed in the setting of consistent, modern imaging. More comprehensive imaging strategies will detect additional disease that would have remained occult in the series on which prognostic scores were based. The prognostic scoring systems also predate effective neoadjuvant chemotherapy. Both radiological and pathological response to chemotherapy are indicators of good prognosis,[48] whereas progression through treatment is associated with a poor prognosis.[49] The majority of clinical scoring systems were derived using patients staged with historical imaging strategies without incorporating treatment response in the analysis. This perhaps explains why these tools are relatively poor discriminators,[19] as illustrated in Figure 2. Here, two patients with similar conventional risk profiles have discrepant clinical outcomes after metastasectomy.

Beyond size and number: novel imaging biomarkers

There is scope for imaging to further characterise tumour phenotypes. Even using conventional CT and MRI, phenotypic variation is observed, both of tumour morphology[50] and in response to chemotherapy[51], while novel imaging techniques can quantify aspects of tumour morphology and physiology that reflect differences in tumour biology.

Tumour response to neoadjuvant chemotherapy

Neoadjuvant chemotherapy may be the first treatment received by patients with oligometastatic disease and, as with treatment of the primary malignancy, pathological tumour response to chemotherapy is associated with improved prognosis.[52] Usually, radiological response, is determined by an objective solid tumour evaluation criteria such as Response Evaluation Criteria in Solid Tumours criteria (RECIST),[53] based on CT or MRI.

At this time, the optimal methodology for using treatment response as a prognostic biomarker for patients with oligometastases has not been established, and response as a prognostic biomarker has not been incorporated into the clinical risk models (see Table 1). Notwithstanding this fact, progressive disease through chemotherapy is a poor prognostic marker and failure to achieve disease control with chemotherapy is usually considered a contraindication to a radical treatment strategy.[49]

Morphological features

The macroscopic histopathological structure of tumours gives rise to the imaging phenotype of conventional imaging, which can be an important indicator of tumour behaviour. Where a robust association between imaging and histopathological features is demonstrated, imaging can be used as an *in vivo*, non-invasive surrogate of tumour biology. This strategy has been used successfully in cancer imaging for validating T- and N-staging in many primary tumour types, and, more recently, for the development and subsequent validation of the MRI feature of extramural vascular invasion (EMVI) in rectal cancer.[54] This was already a recognised histopathological indicator of poor prognosis, and the MRI feature has subsequently been validated as a prognostic biomarker in the clinic.[55]

The same strategy can be applied to oligometastases. Several histopathological features of liver metastases are prognostically relevant, including vascular invasion, presence of a fibrous capsule, tumour regression grade, and the thickness and nature of the tumour-liver interface.[56] The tumour-liver interface, which to some extent reflects tumour angiogenesis,[57] may also have therapeutic implications.[58] For lung metastases, the patterns of intrathoracic spread influence outcome.[59] Imaging has the potential to assess these histopathological features *in vivo*, and to assess lesion-to-lesion heterogeneity.

Observed semantic morphological imaging features, like EMVI, can be assessed subjectively, to produce useful categorical classifications. Although subjective assessment can introduce inter- and intraobserver variation, careful validation can ensure reproducibility, and these semantic features are more readily applicable than quantitative imaging biomarkers across imaging platforms. However, textural analyses, normally based on CT or MRI, can mathematically describe a much greater number of quantitative image properties that underlie visual features.[60] These are attractive as they can be applied to large datasets and, once the methodology established, do not suffer from interobserver variation. Attempts have been made to prognosticate for patients with colorectal cancer based on texture profile of the primary tumour[61] and background liver parenchyma.[62]

Functional tumour imaging

There is a recognised framework[63] for understanding the abnormal biological adaptations that characterise tumours. In the same way that this informs novel therapeutic strategies, it can also provide a framework for novel imaging modalities that may have prognostic and therapeutic implications. Although, in the research setting, imaging techniques, particularly molecular imaging, have been used to assess a wide range of tumour biological processes, there are a small number of functional

imaging techniques which have been investigated in cancer patients and could be readily incorporated in clinical practice.

Vascular imaging

Induction of angiogenesis is an important feature of metastases. Markers of tumour angiogenesis, such as microvessel density (MVD) and vascular endothelial growth factor (VEGF) expression are associated with poor outcomes, for example in NSCLC[64] and colorectal cancer.[65] Perfusion imaging techniques, including dynamic contrast-enhanced MRI (dceMRI) and perfusion CT, use multi-phase image acquisitions following injection of intravenous contrast agents to measure contrast delivery and uptake into tumours. Modeling derived image data produces several metrics, which relate to tumour vascularity and perfusion,[66] although there is heterogeneity of technique and several potential sources of error, particularly for dceMRI.[67] Attempts to correlate these dynamic imaging data with static histological markers of angiogenesis, such as a MVD, have produced mixed results,[67] although response evaluation has been more promising, with several studies reporting correlation of these biomarkers with response to radiotherapy,[68] chemotherapy and antiangiogenic therapy.[69,70] As yet, despite their potential, these techniques are not used for clinical decision-making in the oligometastatic setting.

Metabolic imaging

Deranged glucose metabolism is recognized as a key adaptation of tumour cells.[71] The glucose analogue FDG is widely used in PET-imaging for detecting metastatic disease, and FDG-PET/CT is routinely acquired in some patients with suspected oligometastatic cancer. The standardized uptake value (SUV), a semi-quantitative indicator of metabolic activity, is produced for each voxel, and metrics of tumour metabolic activity and total metabolic tumour burden, the metabolic tumour volume (MTV) and tumour glycolytic volume (TGV), are derived. High metabolic activity and burden has been found to be a poor prognostic marker in several settings, for example in patients with colorectal liver metastases undergoing resection, high SUV and TGV are poor prognostic markers, outperforming multifactor clinical risk scores (Table 1).[72,73] In patients with liver metastases treated with chemotherapy, reduction in FDG-uptake indicates improved prognosis.[74] As yet there is no threshold to allow decision-making based on these data, but novel methods for analyzing PET data may further improve prognostication using this functional imaging tool.[75]

Assessing tumour heterogeneity

Intra- and intertumoral heterogeneity occurs as a result of tumour evolution and clonal expansion.[46] Metastases comprise distinct subclonal populations[76] and greater clonal heterogeneity may be an important determinant of metastatic behavior. Genomic heterogeneity represents a major clinical challenge, both for assessing the diversity of subclonal populations, and for planning effective targeted treatment and

limiting the evolution of resistant clones.[77] For examples, a patient may have two metastases that are biologically distinct, with resultant differences in their response to treatment and subsequent disease behaviour. Assessment of imaging phenotypes by functional or morphological imaging may provide an assessment of this underlying genetic heterogeneity. Furthermore, tumour evolution, under the selective pressure of chemotherapy, produces variable inter- and intratumoral responses. By preserving spatial information, intra- and interlesional variation can be identified. This information could, for example, be used to guide targeted therapy of more aggressive metastases (oligoprogression), or those less likely to respond to systemic therapy. In contrast, invasive biopsies are neither practical nor readily repeatable, for assessing an evolving, multisite disease.

The degree to which intratumoral heterogeneity can be described by imaging will be limited by spatial resolution. Currently, the spatial resolution of clinical CT is as low as 0.5mm, body MRI can achieve in-plane spatial resolution in the region of 1mm, and PET studies produce volumetric data with a resolution of approximately 4mm. This precludes assessment of microscopic tumour features. Image data is a composite of the different tissue types or tracer uptake within each image voxel so it will fail to fully describe features below the image resolution, producing information loss.[78] Small lesions in particular, with fewer voxels in the image produced, and greater proportional partial voluming effects at the boundaries with normal tissues, will be more challenging to assess, although improvements in *in vivo* imaging technology may help to address some of these shortcomings.

Novel approaches for the development and validation of imaging biomarkers

Developing imaging biomarkers for the oligometastatic setting is challenging. Oligometastases may require biomarkers specific to each organ and primary tumour.[79] Differences in the imaging phenotype will occur due to the anatomical location and primary tumour biology, potentially introducing significant variation. As a result, it may prove difficult to validate imaging biomarkers for less common clinical scenarios. Existing biomarkers for oligometastatic cancer have predominantly been derived and confirmed in patient cohorts for higher volume and more established interventions.

Compared with blood or tissue-based biomarkers, imaging biomarker studies have often lacked sufficient sample size for validation, particularly for multivariate analysis alongside established clinical biomarkers. Technological advances and differences in equipment and protocols create inconsistencies in imaging within and between institutions, which are then less readily combined as single datasets. Novel imaging, especially molecular imaging, may be expensive or limited, reducing the potential size of datasets.

There are several emerging strategies to address these issues. One is to use semantic features based on conventional imaging, which are less influenced by variable imaging technique, and this has met with some success. However, there are limitations to the data that can be reliably extracted by visual interpretation. With the computing power now available, it is possible to derive numerous quantitative image features, creating mineable, multiparametric data; this is the evolving field of radiomics.[80] These feature-sets offer the promise of more consistent analysis, which can be more readily incorporated into clinical and trial workflows, and applied to large retro- and prospective populations for clinical validation. Radiomic data then can also be linked to known histopathological or genomic biomarkers, termed radiogenomics.[81] Already, genomic signatures of oligometastatic patients are being described in small cohorts[82-85] The development and validation of prognostic tools based on high-dimensional imaging data linked to clinical and genomic metadata, is promising, and there are ongoing efforts to collate imaging biobanks to provide sufficient substrate for validation. Finally, artificial Intelligence (AI) is the rapidly developing field of computer self-learning, and holds great promise for tumour characterization. It requires large validated datasets, as well as further research into its role in cancer imaging, but, in the future, is likely to help characterise oligometastases more consistently than human observers.

Future Directions

The term oligometastases is now in common clinical use, but remains poorly defined. Novel treatment strategies are widening the therapeutic window for patients defined as having oligometastatic cancer. Old paradigms for selection for metastasectomy[42] are being abandoned as evidence emerges for some, albeit diminishing, benefit in these higher risk groups.[17] As the opportunity to treat metastatic cancer aggressively continues to grow, improved biomarkers to reliably define patients who benefit from these treatments are urgently needed. In the era of precision medicine, these biomarkers may inform future randomised trials.

Imaging already plays an important role in assessing metastatic sites, disease burden and response to treatment. Multimodal imaging should be optimized to provide a comprehensive assessment for each disease setting; it is critical in planning comprehensive multidisciplinary treatment. Conventional imaging biomarkers, in combination with existing clinical, pathological and molecular biomarkers, assist in patient selection for locally directed therapy in the oligometastatic setting. These features will likely remain important prognostic biomarkers, but there are opportunities to extract additional phenotypic information from conventional imaging, which can have prognostic value, while novel imaging techniques can also image specific aspects of tumour biology. It is likely that improved prognostic models will continue to integrate imaging tools with clinical and molecular biomarkers.

However, the capacity for imaging to both characterise *and* localise the phenotypic heterogeneity of multiple tumour sites sets it apart from blood or tissue-based biomarkers, and makes it particularly relevant to the metastatic setting. Novel approaches to existing imaging datasets, and robust biological and clinical validation, will be important in realizing the potential of imaging to guide treatment in the oligometastatic setting.

Key messages

- Oligometastatic cancer is a poorly defined clinical entity, encompassing a broad range of potential sites and primary tumours.
- Identifying oligometastatic cancer may determine whether a patient is considered for locally-directed treatment with radical intent.
- Imaging plays a key role in assessing the extent and site(s) of disease in patients with suspected oligometastatic cancer, which should be optimized according to the primary tumour, site of disease and proposed intervention.
- Imaging biomarkers are already incorporated into prognostic models for defining patients who benefit from radical treatment.
- Novel imaging biomarkers have the potential to assess heterogeneous multisite metastatic disease at multiple timepoints.
- Novel strategies for deriving imaging biomarkers, and linking these to tumour biology, including genomics, can address some of the challenges for their development and validation.

Legends to figures

Figure 1

PubMed publications referring to oligometastases in their title (dark blue) and title and abstract (light blue) by publication year.

Figure 2

FDG-PET/CT studies of two patients with colorectal cancer who developed two Metachronous, unilobar liver metastases. Both underwent hepatic metastasectomy. Patient 1 rapidly developed polymetastatic relapse. Patient 2 remains disease-free.

Search Strategy

We searched PubMed and MEDLINE, and references, for relevant articles published between Jan 1, 1995 and May 30, 2016, in English, with the search terms: “oligometastases”, “oligometastasis”, “oligorecurrence”, “oligoprogression”. The type of study, source of data, and important findings were noted. Selection was based on novelty and relevance to the scope of this Personal View.

Author contributions

JMF – Manuscript preparation and revision
RAS – Manuscript revision
ALH – Manuscript revision
FVG – Article concept and manuscript revision

Conflicts of interest

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