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Review

Imaging to predict checkpoint inhibitor outcomes in cancer. A systematic review

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Abstract ***Background:*** Checkpoint inhibition has radically improved the perspective for patients with metastatic cancer, but predicting who will not respond with high certainty remains difficult. Imaging-derived biomarkers may be able to provide additional insights into the heterogeneity in tumour response between patients. In this systematic review, we aimed to summarise and qualitatively assess the current evidence on imaging biomarkers that predict response and survival in patients treated with checkpoint inhibitors in all cancer types.
Methods: PubMed and Embase were searched from database inception to 29th November 2021. Articles eligible for inclusion described baseline imaging predictive factors, radiomics and/or imaging machine learning models for predicting response and survival in patients with any kind of malignancy treated with checkpoint inhibitors. Risk of bias was assessed using the QUIPS and PROBAST tools and data was extracted.

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Magnetic resonance imaging;
Machine learning;
Deep learning

Results: In total, 119 studies including 15,580 patients were selected. Of these studies, 73 investigated simple imaging factors. 45 studies investigated radiomic features or deep learning models. Predictors of worse survival were (i) higher tumour burden, (ii) presence of liver metastases, (iii) less subcutaneous adipose tissue, (iv) less dense muscle and (v) presence of symptomatic brain metastases. Hazard rate ratios did not exceed 2.00 for any predictor in the larger and higher quality studies. The added value of baseline fluorodeoxyglucose positron emission tomography parameters in predicting response to treatment was limited. Pilot studies of radioactive drug tracer imaging showed promising results. Reports on radiomics were almost unanimously positive, but numerous methodological concerns exist.

Conclusions: There is well-supported evidence for several imaging biomarkers that can be used in clinical decision making. Further research, however, is needed into biomarkers that can more accurately identify which patients who will not benefit from checkpoint inhibition. Radiomics and radioactive drug labelling appear to be promising approaches for this purpose.

1. Introduction

The introduction of immune checkpoint inhibitors has greatly improved survival for patients in advanced stages of several cancer types. Since the approval of checkpoint inhibitors for metastatic melanoma and non-small cell lung carcinoma (NSCLC) in 2011 and 2015 [1,2], respectively, 5-year survival rates have increased from less than 10% to more than 50% and 30%, respectively [3–6]. Checkpoint inhibitors have subsequently been approved for a range of malignancies with similar improvements in survival [7].

However, the effect of checkpoint inhibitors varies significantly from patient to patient. Patients who reach complete or partial remission under therapy have a fair chance of long-term survival or even cure from metastatic disease. In patients with melanoma who responded to a combination of checkpoint inhibitors, median overall survival was 6 years [5]. Non-responding patients, however, experience little-to-no benefit from treatment and have limited survival. For example, only 4% of patients with NSCLC who were alive but showed progression at 6 months were still alive after 4.5 years [7,8].

The prediction of response to treatment is a relevant topic. If non-responding patients can be identified before treatment is started, this can prevent severe and even life-threatening adverse events [9]. These severe events are especially common in patients treated with both anti-PD1 and CTLA-4 inhibitors, occurring in over 30% and 50% of patients with NSCLC and melanoma, respectively [9,10]. Furthermore, accurate patient selection can reduce the high costs associated with check inhibitor therapy, which typically approach 100,000 USD per quality-adjusted life year gained [11]. Lastly, the prediction of non-response is relevant as these patients can, without delay, be treated with other treatments such as targeted therapy [12], or be enrolled in clinical trials investigating novel therapeutic approaches.

To guide treatment decisions, a biomarker must be able to identify non-responding patients with a high specificity. If high specificity is not ensured, the use of this biomarker alone would mean that potentially benefitting patients will not receive treatment. A potential biomarker should, therefore, demonstrate the ability to stratify patients into groups with a marked difference in survival and/or response.

Accurate prediction of response has proven to be a challenge, however, as we do not fully understand why this variation in response exists. Checkpoint inhibition work by blocking proteins (e.g. PD-1, PD-L1 or CTLA-4) that inhibit the body's immune response to tumours [13]. Several crucial factors in anti-tumour response have been explored as predictive markers, such as PD-L1 expression, presence of tumour infiltrating lymphocytes and tumour mutational burden [14,15]. Clinical biomarkers, for example stage of disease, WHO performance status, neutrophil-to-lymphocyte ratio, and level of lactate dehydrogenase have been examined as well. None have, however, proven to be accurate enough to select patients who should not be treated with checkpoint inhibition [16]. Patients with NSCLC may, for instance, respond to anti-PD1 treatment even though PD-L1 expression is absent [17].

Imaging may be able to provide additional insights into the heterogeneity in tumour response between patients. The underlying rationale for this hypothesis is that different tumour genotypes will be expressed as different imaging phenotypes. Readily available baseline imaging may therefore provide potentially valuable information about tumour size, tumour/metastasis location and, if acquired, fluorodeoxyglucose positron emission tomography (FDG-PET) parameters. Furthermore, the measurements of lesion shape, intensity and texture on imaging can potentially capture information about the tumour phenotype. These measurements, collectively known as radiomics, may then subsequently be correlated to clinical outcomes [18].

Lastly, radioactive labelling of checkpoint inhibitor molecules can provide insight into the drug uptake throughout the body including in the tumour [19].

To our knowledge, no comprehensive review has been published on the entire spectrum of prognosis research in imaging biomarkers and outcome to checkpoint inhibitors across malignancies. Earlier publications were dedicated to either a single modality (e.g. PET imaging or radiomics) or a single malignancy [20–23]. This limits a complete overview, as advancements in one disease may very well be applicable in another. Furthermore, the predictive value of more sophisticated modalities (e.g. radiomics) should be compared to that of simple markers (e.g. tumour burden) to see if they add value. With this comprehensive review, we aim to fill this gap and facilitate future research.

In this work, we aimed to systematically review the ability of different imaging modalities to predict response to checkpoint inhibitors. The population of interest consists of patients treated with any checkpoint inhibitor for any malignancy. Investigated predictors are any individual biomarkers derived from imaging modalities and models including these. The outcomes of interest are response (according to RECIST [24] or iRECIST [25] criteria), progression-free survival (PFS) and overall survival (OS). Both prognostic and predictive factors are examined. A prognostic factor provides information about a future outcome irrespective of therapy (e.g. tumour stage for OS). In contrast, a predictive factor forecasts the effect of a specific treatment (e.g. oestrogen receptor status for tamoxifen in patients with breast cancer) [26]. Despite this difference, prognostic factors are still important in guiding treatment decisions: preventing unnecessary side-effects and costs in a patient due to a very poor prognosis is no less valuable than doing so based on a pure predictive factor. For this reason, both types of factors were investigated.

2. Methods

This systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [27]. Details of the protocol for this study were registered on PROSPERO and can be accessed at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42020186199.

2.1. Selection of studies

On 29th November 2021, the PubMed and Embase databases were searched for relevant studies. Other data sources were publications found from references of selected articles. Also, to ensure sensitivity of the search strategy and to identify additional relevant studies, Scopus was used. No date restrictions were applied on the systematic searches and included articles published on 29th November 2021.

Inclusion criteria for eligible articles were original full-text research articles describing baseline imaging prognostic factors and radiomics and/or imaging prediction models (e.g. using machine learning) for response and survival in patients treated with anti-PD1 checkpoint inhibition with any kind of malignancy above 18 years of age.

The literature search used the following terms (with synonyms, MeSH terms, and closely related words): 'immunotherapy' or 'immune checkpoint inhibitor' combined with 'radiological', 'baseline factors' and 'predictive', or combined with 'radiomics' or 'machine learning'. We specifically adopted a broad search to include all articles related to imaging and predictive factors and to radiomics and machine learning studies. Duplicates were removed using EndNote. The complete search strategy is listed in Supplementary file 1.

All articles were screened for relevance. Studies only reported as conference abstracts without published full-text reports were not included owing to the inability to completely assess validity and methodologies. Other exclusion criteria were case reports, reviews and meta-analyses. The search was restricted to studies in human participants and papers written in English. Furthermore, studies only reporting predictive factors, radiomics or machine learning models based on on-treatment imaging (instead of pre-treatment imaging) were excluded.

2.2. Screening process

Titles and abstracts were screened for relevance by two reviewers (ID and LM) using the Rayyan QCRI web application [28]. Articles were excluded if they did not meet the inclusion criteria. Next, the selected full-text articles were assessed for eligibility by the same reviewers. Subsequently, the final selection of studies was made (Fig. 1).

2.3. Critical appraisal

Two tools were used to evaluate the risk of bias: the QUIPS tool [29] was used to assess studies reporting individual prognostic or predictive factors; the PROBAST tool [30] was used to assess studies constructing models that make predictions for individual patients.

The QUIPS tool is specifically designed to assess the risk of bias in prognostic factor studies and does so by judging the quality of a prognostic factor study on six key domains: 'study participation', 'study attrition', 'prognostic factor measurement', 'outcome measurement', 'study confounding' and 'statistical analysis and reporting'. The domain 'study attrition' was not evaluated, as almost all studies were retrospective cohort studies that did not report on loss to follow-up during the data collection period. This domain could therefore not be accurately assessed and was consequently not used. Adaptation of the QUIPS tool for specific

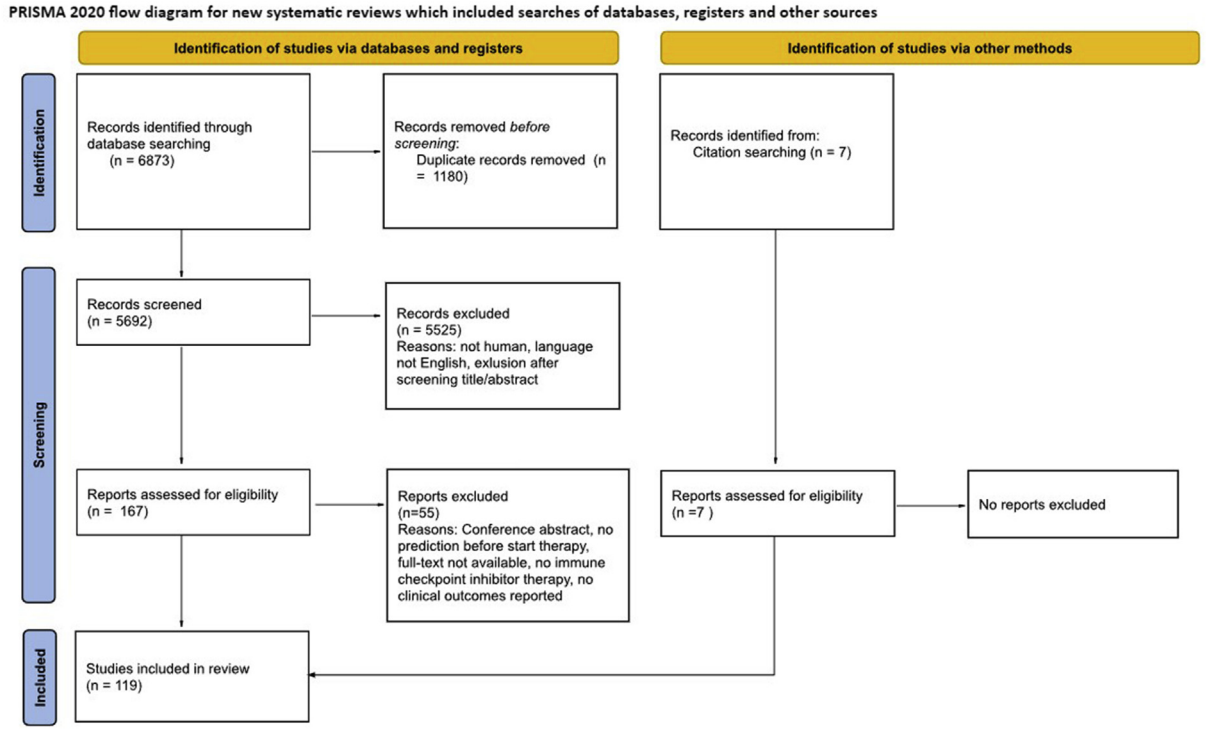

Fig. 1. PRISMA flow chart of article screening and selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

purposes is encouraged by the developers in the accompanying article [29].

The PROBAST tool is designed to judge the risk of bias in studies on models that make predictions for individual patients. As the PROBAST tool was developed for the appraisal of regression-type models, the authors recommend the use of additional signalling questions when evaluating studies on machine learning models [30]. The statistical analysis domain of the PROBAST tool was therefore augmented with the following three questions: (i) 'Is all data from a single patient reserved to only a single data partition (e.g. training, testing or tuning)?', (ii) 'Is the optimal model selected and are hyperparameters tuned?' and (iii) 'Is only the best model evaluated on the independent validation set?' (see Supplementary file 2). The remaining domains ('Participants', 'Predictors' and 'Outcome') were not altered.

In addition to the risk of bias assessment, the Radiomics Quality Score (RQS) was used to evaluate study quality in all studies reporting on quantitative imaging-derived features (radiomics) [163]. All quality assessments of the included studies were done by two independent reviewers (ID and RM). Any disagreement was resolved through discussion.

2.4. Data extraction

The following details were extracted from the studies: total number of patients investigated, cancer type, study treatment and design, imaging modality (computed tomography (CT), magnetic resonance imaging (MRI) or PET/CT), results and corresponding significance and outcome. Both response to therapy (odds ratio or comparison between groups resulting in a p-value) and survival parameters (hazard ratio for progression-free survival and overall survival) were obtained for the individual predictor studies. In the prediction model studies, an area under the curve or sensitivity and specificity of the model was stated, this information was also collected. For radiomics and machine learning studies, the size of the training- and validation cohorts were extracted as well.

2.5. Synthesis

The investigated prognostic factors and prediction models were grouped into six categories: tumour burden, body composition, location, FDG-PET features, other radioactive tracer imaging and radiomics. Extracted characteristics and results from all studies were grouped according to category, marker and disease. A quantitative meta-analysis was not considered feasible due to heterogeneity in population, predictor definitions and reported outcomes. The available evidence was therefore summarised based on (in order of importance) study quality, consistency of the results across studies and sample size.

3. Results

3.1. General characteristics

The search yielded 6873 records from databases and 9 through reference screening. A total of 119 studies

Table 1
Summary of findings.

Category	Biomarker	Study results	N	Cancer(s)	Reference
Tumour burden	Higher tumour burden	↓ OS, PFS	303, 103, 21, 83, 96, 58, 583, 37, 1461	Melanoma, NSCLC, HNSCC	[32,34,35,36,37,41,42,43,45]
		↓ Response	303	Melanoma	[32]
		No effect on OS, PFS or response	111, 140, 85, 251, 49, 9	Melanoma, NSCLC, RCC, various	[31,33,38,39,40,44]
	Higher number of metastases	↓ OS, PFS	183, 303, 201	Melanoma, NSCLC	[46,32,48]
		↓ Response	303	Melanoma	[32]
		No effect on OS, PFS or response	520, 80, 58	Melanoma, NSCLC	[47,49,41]
Body composition	More visceral adipose tissue	↓ OS, PFS	133	Melanoma	[53]
		↑ OS	55	NSCLC	[50]
		↑ PFS	70, 79	Urothelial carcinoma	[52,51]
		No effect on OS, PFS or response	74, 117, 153, 147	NSCLC, various, melanoma	[54,55,56,57]
	More subcutaneous adipose tissue	↑ OS	55, 70	NSCLC, urothelial carcinoma	[50,52]
		↑ OS, PFS	90	Various	[58]
		↑ OS, PFS and response	79	RCC	[51]
		No effect on OS, PFS or response	117, 153, 147	Melanoma, various	[55,56,57]
	Higher skeletal muscle quantity	↑ OS	36, 100	NSCLC, various	[59,66]
		↑ PFS	149	Gastric cancer	[65]
		↑ PFS and response	42, 28	NSCLC	[61,63]
		↑ OS, PFS	61, 27	HNSCC	[62,64]
		↑ OS, PFS and response	103	NSCLC	[60]
		No effect on OS, PFS or response	133, 287, 23, 46, 74, 156, 117, 251, 88	Melanoma, NSCLC, various	[53,67,68,69,54,70,55,39,71]
	Higher skeletal muscle density	↑ OS	44, 90	Melanoma, various	[72,58]
		↑ PFS	156, 147	NSCLC, melanoma	[70,57]
		↑ Response	133	Melanoma	[53]
		↑ OS, PFS and response	70	Urothelial carcinoma	[52]
		No effect on OS, PFS or response	287, 79, 100, 88, 74	NSCLC, melanoma, renal cell carcinoma, various	[67,51,66,71,54]
Location	Liver metastasis	↓ OS, PFS	140, 336, 514, 201, 296, 58, 172, 90	Melanoma, NSCLC, various	[33,74,47,48,75,41,79,78]
		↓ Response	315, 140, 583, 336	Melanoma	[73,33,42,74]
		No effect on OS, PFS or response	303, 213, 80	Melanoma, NSCLC	[32,76,49]
	Lung metastasis	↑ PFS	140	Melanoma	[33]
		↑ ORR	140, 583	Melanoma	[33,42]
		↓ PFS	201	NSCLC	[48]
		No effect on OS, PFS or response	336, 303, 213, 9, 172, 90	Melanoma, NSCLC, RCC, various	[74,32,76,78,79,78]
	Lymph node metastasis	No effect on OS, PFS or response	140, 303, 201, 90	Melanoma, NSCLC, various	[33,32,48,78]
	Brain metastasis	↓ OS	168, 291	Melanoma, various	[47,82]
		No effect on OS, PFS or response	336, 303, 92, 201, 58, 296, 213, 172, 90	Melanoma, NSCLC, various	[32,41,48,74–76,78,79,81]
	Symptomatic brain metastasis	↓ OS	514	Melanoma	[47]
	Bone metastasis	No effect on OS, PFS or response	140, 303, 213, 58, 201, 172, 90	Melanoma, NSCLC, various	[32,33,41,48,76,78,79]
	Pleural effusion	↓ PFS	213	NSCLC	[76]
		No effect on OS, PFS or response	296, 201	NSCLC	[48,75]
FDG-PET	Higher SUVmax/mean	↑ Response	89, 63	NSCLC	[84,77,98]
		↓ Response	32, 111	NSCLC	[87,31]
		↓ OS	34	Melanoma	[86]
		↑ PFS	63	NSCLC	[77]
		↓ PFS	105, 30	HNSCC	[89,90]
		No effect on OS, PFS or response	9, 92, 40, 55, 80, 85, 90, 111, 63, 92, 32, 49, 30,	NSCLC, RCC, melanoma, various	[44,81,83,85,49,38,88,31,77,81,40,90]

Table 1 (*continued*)

Category	Biomarker	Study results	N	Cancer(s)	Reference
	Higher metabolic tumour volume	↓ OS, PFS	55, 85, 112, 56, 80, 63, 105	NSCLC, Melanoma, HNSCC	[38,46,49,50,85,92,93]
		↓ Response	56, 55, 80, 63	Melanoma	[49,77,85,93]
		↑ Response	105	HNSCC	[89]
		No effect on OS, PFS or response	92, 40, 34, 32, 49, 90, 30	NSCLC, Melanoma, Lymphoma, RCC	[40,81,83,86–88,90]
	Higher total lesion glycolysis	↓ OS	56, 34, 85	Melanoma	[93,86,38]
		↓ Response	55	Melanoma	[85]
		No effect on OS, PFS or response	92, 90, 111, 32, 49, 40, 63, 30	Melanoma, NSCLC, various	[81,88,31,87,40, ,83,77,90]
Other tracers	Higher total lesion sodium fluoride	↓ OS	111	Genitourinary tumours	[94]
	Higher Zr-atezolizumab SUVmax	↑ OS, PFS	25	Various	[96]
	Higher Zr-pembrolizumab SUVmax	↑ Response, PFS	18	Various	[97]
		↑ Response	12	NSCLC	[98]
	Higher uptake of [F] FB-IL2	No effect on OS, PFS or response	13	Melanoma	[100]
	Higher Zr-durvalumab SUVpeak	No effect on OS, PFS or response	13	NSCLC	[99]
	Higher 18F-BMS986192 tumour-to-blood ratio	↑ Response	8	Melanoma	[101]
	Higher F-fluorothymidine SUVmean	No effect on OS, PFS or response	17	Prostate cancer	[95]
Radiomics	Various individual radiomics	Predictive of OS	105, 31, 103, 48	Melanoma brain metastasis, melanoma, renal cell carcinoma	[102,103,34,109]
		Predictive of PFS	54, 60, 104	Melanoma, NSCLC	[104,105,106]
		Predictive of OS, PFS	21	NSCLC	[107]
		Predictive of response	112	NSCLC	[108]
	Radiomics models	Predictive of response	70, 66, 203, 63, 11, 30, 22, 83, 48, 75, 64, 86, 57, 254, 409, 94	Melanoma, NSCLC, HNSCC, Urothelial carcinoma, renal cell carcinoma, overian carcinoma, oesophageal squamous cell carcinoma, hepatocellular carcinoma, various	[112,22,114,119, 121,124,127,128,130, 132,133,135,136, 137,138,139]
		Predictive of OS, PFS	46, 83, 332	NSCLC	[115,118,123]
		Predictive of OS	38	Lung adenocarcinoma	[125]
		Predictive of PFS	297, 289, 47, 31, 68	NSCLC, urothelial carcinoma, various	[116,117,122,129,135]
		Predictive of response, OS and PFS	92	NSCLC	[120]
		Not predictive of response	50, 257	Melanoma, NSCLC	[22,111]
	Deep learning models	Predictive of response	803, 151, 54, 41	NSCLC, lung adenocarcinoma, urothelial carcinoma	[144,142,141,140]
		Predictive of PFS	938	NSCLC	[145]
		Predictive of OS, PFS	573	NSCLC	[144]

Notes: 'No effect' is defined as 'no statistically significant effect demonstrated'.

remained after title/abstract screening (Fig. 1). These studies are listed in Supplementary Table S1. The studies included a total of 15,580 patients, with a median sample size of 74 (range 8–1461). The most studied malignancy was NSCLC (42 studies), followed by melanoma (33 studies) and urothelial carcinoma (seven studies). All but one study investigated patients with metastatic disease.

The predictive value of tumour burden was investigated by 19 papers; body composition by 24 papers; metastasis location by 18; FDG-PET features by 21; other traces by 8; radiomics by 45 papers; models other

than radiomics by two (Supplementary Table S1). All studies reporting on factors in the first five categories and nine radiomics studies investigated individual predictive factors. These studies were therefore assessed for the risk of bias using the QUIPS tool (Supplementary Table S2). The remaining studies reported the performance of predictive models and were assessed for the risk of bias using the PROBAST tool (Supplementary Table S3). One study reported both on individual predictive factors and on a model and was assessed using both tools. The results of the RQS screening are shown in Supplementary Table S4. Data extraction results are given per category in Supplementary Tables S5–S11. A summary table of all results is provided in Table 1. A discussion of the two papers describing predictive models without the use of radiomics is provided in Supplementary file 3. For the other categories, an overview of the results is provided below.

3.2. Tumour burden

Measures of tumour burden (defined as the total amount of cancer in the body) were grouped into two categories: measures of total tumour volume (e.g. sum of largest diameters, sum of volumes) and tumour count (either number of metastases or number of affected organs). Although volume and tumour count are expected to be correlated in patients, these measures may diverge in patients with many small metastases. As this specific pattern of metastases may indicate different tumour biology, count and volume were considered separately.

Measures of tumour volume were investigated in 15 studies [31–44]. Nine studies indicated that a higher tumour volume was associated with worse survival across tumour types [32,34–37,41–43,45]. These included the three studies with the largest sample size ($n = 1461$, $n = 583$ and $n = 303$) and a low risk of bias [32,42,45]. Hopkins *et al.* ($n = 1461$) reported a hazard rate ratio (HR) of 1.64 for overall survival per decimetre increase of the sum of diameters of target lesions in patients with NSCLC [45]. Similarly, Joseph *et al.* ($n = 583$) reported a HR of 1.64 for overall survival in patients with melanoma and with a sum of diameters above the median [42].

Six studies reported on the number of metastases as a prognostic factor [32,41,46–49]. In univariate analysis, this factor was a significant prognostic factor for survival in three studies [32,46,48] with a trend towards significance in a fourth [49]. In multivariate analysis, this effect remained significant only in one paper [46].

3.3. Body composition

Metrics of body composition were divided into four categories, namely visceral adipose tissue, subcutaneous adipose tissue, skeletal muscle quantity and skeletal muscle density.

The eight papers reporting on the metrics of visceral adipose tissue showed conflicting findings: three papers demonstrated improved survival [50–52], whereas one paper reported worse survival in patients with melanoma and with more visceral adipose tissue [53]. The remaining papers reported no significant association with survival [54–57]. Furthermore, there were considerable methodological concerns: one paper [50] was at low, one [57] at moderate, five [51–53,55,56] at high and one [54] at an unclear risk of bias.

Seven papers investigated the predictive value of subcutaneous adipose tissue. The results indicated either better (4 papers) [50–52,58] or equal (3 papers) [55–57] survival in patients with higher amounts of subcutaneous fat, with HRs for OS ranging from 0.2 to 1 at varying thresholds. Five papers [51,52,55,56,58] were at high risk of bias, primarily due to the use of data driven optimised thresholds without validation. The risk of bias of the remaining two papers was low [50] and moderate [57].

Seventeen papers reported on various measures of skeletal muscle quantity. Eight papers demonstrated that higher skeletal muscle quantity was associated with better survival [59–66]; the remaining nine papers reported no significant correlation [39,53–55,67–71]. Reported HRs for overall survival ranged from 0.75 to 2.99. Risk of bias was low in 3 [61,64,67], high in 10 [39,53,55,59,63,65,66,68,70,71] and unclear in 4 papers [54,60,62,69], data driven thresholds again being the most common concern.

The influence of skeletal muscle density was investigated by 11 papers. Five papers indicated that higher skeletal muscle density was associated with a better survival [52,53,57,70,72]; six papers reported non-significant findings [51,54,58,66,67,71]. One paper [67] was at low, one [57] at moderate, eight [51–53,58,66,70–72] were at high and one paper [54] at unclear risk of bias.

3.4. Metastasis location

In 14 papers, the presence of liver metastases was investigated [32,33,41,42,47,48,73–80]. These papers indicated that liver lesions were associated with worse survival across all tumour types, with HRs between 1.6 and 1.9 for progression-free survival in the three highest quality studies [47,48,74]. Additionally, radiological response to treatment appeared to be lower in patients with melanoma and with liver metastases (odds ratios between 0.3 and 0.6) [33,42,73,74]. Results describing the correlation with response in other tumour types were not provided or showed no significant findings. Overall study quality varied: five studies [42,47,48,73,74] were at low risk, one [77] at high risk and eight [32,33,41,75,76,78–80] at unclear risk of bias.

Thirteen of the included studies investigated the presence of brain metastases [32,33,41,47,48,74–76,78–82]. The presence of brain metastases was not found to be a significant predictor of inferior outcomes in most studies.

A notable exception was the largest and only real-world study on this topic by Van Zeyl *et al.* ($n = 583$) in advanced melanoma, which showed that brain metastases in the presence of symptoms were associated with worse overall survival (HR 1.91) [47]. The quality of included studies was reasonable: three studies [47,48,74] were at low risk, one [82] at high risk and nine [32,33,41,75,76,78–81] at unclear risk of bias.

Other investigated tumour locations were bone [32,33,41,48,76,78,79], lung [32,33,42,44,48,74,76,78,79], pleural effusion [48,75,76], lymph node [32,33,48,78], soft tissue [32,33], gastrointestinal [33], adrenal [33,76] and spleen [33]. None of these locations appeared to be a consistent and independent predictor of response or survival.

3.5. FDG-PET features

Several FDG-PET features were investigated as potential predictors. The most reported features were standardised uptake value (SUV) (15 studies), (total) metabolic tumour volume (16 studies) and total lesion glycolysis (10 studies).

Sixteen studies examined SUVmax and SUVmean of the primary lesion and metastases as prognostic factors [31,38,40,44,49,77,81,83–91]. The findings of the included studies indicated that neither SUVmax nor SUVmean were robust predictors of survival: reported significant findings were sparse and conflicting. Furthermore, risk of bias was substantial: one study [38] was at low, nine studies [31,40,49,77,83,85–87,89] were at high and six studies [44,81,84,88,90,91] at unclear risk of bias.

Sixteen studies investigated total metabolic tumour volume [38,40,46,49,50,77,77,81,83,85–90,92]. Of these, eight studies demonstrated significantly worse survival in patients with higher metabolic tumour volume [38,46,49,50,77,85,92,93]. This included the largest study by Awada *et al.* ($n = 112$), which was at a low risk of bias and reported a HR for OS of 1.004 per mL [46]. Considerable methodological concerns existed in the remaining studies: risk of bias was low in three studies [38,46,50], high in ten studies [40,49,77,83,85–87,89,90,92,93] and unclear in three [81,88,90]. Furthermore, two of the studies had at least a partial overlap in study population [85,93].

Total lesion glycolysis, which is the product of SUV and metabolic tumour volume, was investigated by 11 studies [31,38,40,77,81,83,85–87,90,93]. It combines volumetric and metabolic information, and therefore presumably contains more information on the tumour than SUV and morphological tumour value (MTV). Four articles reported a significant association of total lesion glycolysis with survival [38,85,86,93], three of which studied patients with melanoma [85,86,93]. Findings were not significant in the other studies. Overall risk of bias was similar to the previous markers: one study [38] was at a low risk of bias, 8 studies [31,40,77,83,85–87,93] were at high risk and two studies [81,90] at unclear risk of bias.

3.6. Other PET radioactive tracers

Other investigated tracers included sodium fluoride, F-fluorothymidine and Zirconium labelled to different anti-PD1 antibodies, namely atezolizumab, pembrolizumab and durvalumab.

Lim *et al.* investigated total lesion fluoride in genitourinary tumours and found this feature to be a significant prognostic factor for overall survival (HR 2.64) [94]. Scarpelli *et al.* investigated the relation between tumour SUVmean and SUVtotal in F-fluorothymidine PET-CT. Neither feature was significant in the multivariate Cox-regression [95]. Furthermore, both studies were judged to be at a high risk of bias due to inadequate correction for known predictors.

Bensch *et al.* prospectively investigated the predictive value of Zirconium-labelled atezolizumab in various tumour types [96]. They found that the increased uptake of labelled atezolizumab corresponded to a better response to atezolizumab at first assessment and better overall and progression-free survival (HR 6.3 and HR 11.7, respectively).

Zirconium was also used to label pembrolizumab [97,98] and durvalumab [99]. Similar results were found in these studies: increased uptake to labelled anti-PD1 corresponded with higher response and survival.

An interesting approach was performed by Van de Donk *et al.* Interleukin-2 was labelled to fluorine-18, in order to visualise T-cell activity by tumour infiltrating T-cells who express the high-affinity interleukin-2 receptor [100]. The tracer was safe; however, no correlation with response to therapy could be found possibly due to including only 13 patients.

Another way to visualise mechanisms of PD1 inhibitors on a cellular level was carried out by Nienhuis *et al.* [101]. They performed PET imaging in eight patients with metastatic melanoma and with a tracer that visualises PD-L1 expression on the tumour. This pilot study indicated that baseline tracer uptake was associated with change in lesion size at follow-up when normalised for tracer availability in the blood pool (*Pearson's* $r = -0.43$).

3.7. Radiomics

Studies investigating radiomics were grouped according to their methodology: nine studies investigated the value of individual radiomic features; 30 studies constructed a (machine learning) model based on extracted radiomic features and six studies trained a deep learning model.

The quality of the nine studies [34,102–109] investigating individual radiomic features was judged to be

poor, as reflected in both the QUIPS rating and RQS score. Primary concerns were use of optimal thresholds, lack of independent validation and absence of correction for known predictors. Furthermore, all studies reported a significant finding, although none of the radiomic features were so far reproduced or validated in an independent study. Thus, no solid evidence exists for the predictive value of any single radiomics marker.

Similarly, all but two [110,111] of the 30 studies [110–139] that constructed a radiomics model reported a positive finding. The median reported area under the curve for predicting response was 0.787 (range 0.52–0.963). However, numerous methodological concerns exist for these studies as well. First, a significant fraction of studies was at high ($n = 15$) or unclear ($n = 6$) overall risk of bias. The most common flaws were lack of correction for overfitting (ten studies) and a lack of transparency regarding model selection and tuning (11 studies). These weaknesses were affirmed by the low overall RQS, with a median score of ten out of a maximum of 36. Second, most studies had a limited sample size (median $n = 68$). Third, the three studies with the highest RQS ($RQS = 24$, 18 and 14) and largest sample size ($n = 289$, 210 and 332) appeared to have a significant overlap in patient population [116,117,123]. These studies can therefore not be considered independent. Lastly, the predictions of the only radiomics model [138] that has been validated in subsequent studies [135,139] correspond closely with the presence of liver metastasis, which is a known predictor of worse outcome. As the authors did not correct for this predictor, the added value of this model is unclear and needs to be further investigated.

Six studies investigated deep learning radiomics models. Three studies were judged to be at a high risk of bias and had only small validation cohorts (41, 12 and 29 patients) [140–142]. In the three remaining studies, the risk of bias was judged to be low, size of the validation set was adequate ($n = 123$, 187 and 94) and the RQS was at or above the median (13, 15 and 10) [143–145]. Two of these studies appeared to have an overlap in study population [143,144]. Notably, all three studies reported on a deep learning model that was trained to predict an intermediate variable (PD-L1 expression, tumour mutational burden or EGFR mutation); patients could subsequently be stratified into risk groups with a HR for PFS of, respectively, 1.78 and 2.57 and OR for response of 2.03.

4. Discussion

4.1. Overview

The objective of this review was to identify imaging biomarkers in prognosis research in all patients with cancer and treated with checkpoint inhibitors. Based on the findings of the included studies, several groups of predictors were identified with varying strength and quality of evidence.

Higher tumour burden is very likely to be predictive of worse survival. This finding is consistently supported across tumour types by the highest quality studies on this topic. It also corresponds to our knowledge in other oncological populations undergoing other types of treatment [146–148]. Furthermore, there is a reasonable biological basis. First, higher tumour burden leads to sicker patients, and they are therefore more likely to succumb before they experience benefit from treatment. Second, hypoxia plays a bigger role in larger necrotic masses. Hypoxia is associated with immune escape and therefore worse response [149–151]. However, despite the correlation between tumour burden and survival, the reported effect sizes indicate that this marker is not strong enough to guide treatment decisions by itself and there is also insufficient evidence that tumour count adds predictive value to tumour volume.

Higher amounts of subcutaneous adipose tissue may be associated with better survival. Although the findings on visceral adipose tissue are conflicting, the results on subcutaneous adipose tissue are consistently in accordance with the so-called ‘obesity paradox’, in which a high body mass index appears to be a protective factor in cancer patients [152–155]. It must be noted, however, that the reported results may be an overestimation of the true effect, as reflected in the risk of bias assessment. Furthermore, it is unknown whether the value of this predictor is independent from simple clinical metrics, such as body mass index. It is therefore deemed unlikely that this marker will further impact clinical decision making in the near future.

More and denser muscle may be predictive of better survival. The findings of the included studies on this topic are supported by similar observations in other oncological populations [156–158]. Again, however, there is a risk that the observed effect is an overestimate due to biased analysis. Furthermore, the reported effect sizes appear to be smaller in the larger studies, indicating that publication bias may play a role. In conclusion, the association of muscle density and quantity with survival is plausible as they indicate fitter patients with more reserve, but currently investigated parameters may be only of limited predictive value.

The presence of liver metastases is shown to be a marker of worse survival across cancer types. This marker, too, is an indicator of more advanced disease with spread to the visceral organs. Interestingly, several large, high-quality studies in patients with melanoma show that the presence of liver metastases also predicts worse response compared to metastasis in other organs. Whether this is due to liver metastases being less responsive, or to patients with liver metastases being innately different, is the topic of an emerging field of research. In pre-clinical models, several hepatic cell types have shown to modulate T-cells in the

liver and create a systemic immune desert [159]. Furthermore, systemic T-cell loss and diminished immunotherapy efficacy has been observed in patients with liver metastases [159].

Symptomatic brain metastases may be associated with worse survival in melanoma. No significant impact of the presence of asymptomatic brain metastases was observed in most of the included studies. However, almost all included studies on this topic investigated trial populations, in which patients with brain metastases were excluded. The study conducted by Van Zeyl at el., however, examined real-world data and demonstrated that symptomatic brain metastases were associated with worse survival in patients with melanoma [47]. As previous studies have shown that checkpoint inhibitors are effective against brain metastases, this difference in survival is likely to be caused by more frequent neurological complications [160].

The added value of baseline FDG-PET features in predicting response to treatment seems to be limited. Of the investigated PET features, only a higher total MTV was consistently shown to be associated with worse survival. However, since metabolic and MTV are at least partly associated and none of the included studies corrected for morphological tumour burden, it is unclear if MTV is of added predictive value. Significant findings about other FDG-PET-derived metrics (SUVmax, SUVmean and TLG) are scarcer and were often at a high risk of bias.

Radioactive drug labelling appears promising, although current evidence is very preliminary. The hypothesis that uptake corresponds to response has a very strong biological basis. Furthermore, the reported results from small pilot cohorts are promising. However, it remains to be investigated if the positive results will generalise to larger sample sizes and if they will be independent of known predictors.

The value of radiomics remains unknown due to the lack of high-quality evidence. Although the results of the included papers on radiomics are almost exclusively positive, the reported findings are likely to be overoptimistic for several reasons. First, methodological flaws may have led to an overestimation of the predictive value of the described models. Second, the aggregated results are likely to be additionally affected by publication bias. Arguably, studies into radiomics are at an even higher risk of publication bias: while negative findings about traditional markers may be informative, a negative finding about a radiomics model can be viewed as 'a complex machine that does not work'. This, in combination with limited sample sizes in included papers and repeated publications on very similar datasets, may have considerably skewed the aggregate results. Third, many radiomics features are sensitive to variation in scanner type and protocol between centres [161]. This variation may therefore reduce the predictive value of the proposed models to only a fraction of what is shown. In conclusion, the positive findings of the few high-quality papers are promising, especially those that use an intermediate endpoint for training. These findings, however, remain to be confirmed through external and prospective validation.

4.2. Future research

The predictive value of imaging biomarkers may improve through future developments. Specifically, we believe that subsequent research should focus on three key areas. First, imaging biomarkers should be integrated with predictors from other modalities. As no single biomarker has yet been proven to be sufficient for effectively guiding treatment decisions, we must investigate combinations of multiple – uncorrelated – predictors. Concretely, this can be envisioned as a multivariate prediction model combining imaging biomarkers with clinical, histological, biochemical and genetic predictors, among others. Second, the added value of radioactive drug labelling should be explored in larger studies. These studies should also particularly report on the added value of this biomarker over known predictors. In addition, negative results about these markers would also be very beneficial in advancing the field of research due to the efforts and costs needed to produce these tracers. Third, new studies should more closely adhere to methodological guidelines and should confirm previous findings through rigorous validation. This is especially the case for radiomics studies, of which the impact is currently limited by methodological shortcomings. If, however, radiomics are proven to be independent predictors, they would be able to provide us with valuable information at no additional cost or harm to the patient.

4.3. Limitations

The first main limitation of this review is the lack of a universally agreed upon tool to assess the risk of bias in machine learning studies. We used a combination of the PROBAST tool and RQS to assess the quality of the radiomics studies. Both tools, however, have limitations for this purpose. The PROBAST tool addresses most domains that put a machine learning model at a risk of bias, but not all. The PROBAST-AI tool is currently under development to meet this need [162]. Furthermore, the RQS provides excellent guidance in the design of a good radiomics study but is not intended for scrutinising papers to detect a possible risk of bias.

The second main limitation is the lack of a quantitative meta-analysis due to the differences in definition of predictor or outcome in the included studies. Significant variation regarding predictors exists, often caused by dichotomising continuous values at various thresholds. This, in combination with the fragmentation of evidence across different diseases and treatments, makes a quantitative analysis essentially impossible. We were

therefore unable to quantify the predictive power of the investigated markers. We do, however, think that there is enough ground for the conclusion that no individual imaging-based biomarker is proven to be sufficient.

5. Conclusion

In conclusion, there is well-supported evidence for several imaging biomarkers of response to checkpoint inhibitors. Especially, higher tumour burden and the presence of liver metastases are demonstrated to be predictors of worse outcomes across malignancies and drugs. However, none of these single predictors seem strong enough to reliably identify patients that will not derive benefit from treatment. A high degree of accuracy is required for this purpose, as falsely designating a patient as a non-responder would deny a patient access to long-term ICI. Radiomics and radioactive drug labelling appear to be very promising, although reported findings on these approaches should be regarded as preliminary at this moment. In addition to further validation of these methods, future research should focus on integrating imaging biomarkers with predictors from other modalities in high-quality and sufficiently large independent cohorts.

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Conflict of interest statement

PD has consultancy/advisory relationships with Paige, Pantarei and Samantree paid to the institution and research grants from Pfizer, not related to current work and paid to institute. KS has advisory relationships with Bristol Myers Squibb, Novartis, MSD, Pierre Fabre, AbbVie and received honoraria from Novartis, MSD and Roche.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.07.034.

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