The relationship between tumour glucose metabolism and host systemic inflammatory responses in patients with cancer: A systematic review

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ABSTRACT

Introduction: One of the most important and long recognised characteristics of tumour cells is their dysregulated cellular energetics with anaerobic driven glucose uptake. In patients with cancer the prognostic value of the systemic inflammatory response has been well established and the recent combination of PET and CT scanning combines the assessment of tumour physiological activity with detailed anatomical localisation. The aim of this study was to carry out a systematic review of the assessment of the relationship between both the tumour and host inflammatory responses using PETCT.

Methods: An extensive literature review using targeted subject headings was carried out in the US National Library of Medicine, the Excerpta Medica database and Cochrane Database of Systematic Reviews until the 31st March 2018. On completion of the online search, the title and abstracts of each identified study was examined for relevance. Studies with duplicate datasets, not available in English and that did not have full text availability were excluded. Full texts of relevant articles were obtained and were then examined to identify any further relevant articles.

Results: Twelve studies containing 2,588 patients were included in the final analysis. All of the included studies used the 18FDG tracer in PETCT imaging and had biochemical assessment of the systemic inflammatory response. The majority of studies showed a direct relationship between the tumour and bone marrow glucose uptake and host systemic inflammatory responses as measured by C-Reactive Protein (CRP) (n=2), albumin (n=2), White Cell Count (WCC) (n=3), neutrophils (n=2) and platelets (n=2). The majority of the studies (n=8) also showed a direct relationship between tumour and bone marrow glucose uptake and poor outcomes.

Conclusion: This review suggests a direct relationship between the tumour and bone marrow glucose uptake and host systemic inflammation. This may suggest new

approaches for more optimal therapeutic targeting and monitoring strategies in patients with cancer.

Keywords: Systemic inflammation, Cancer, Glasgow Prognostic Score, Neutrophil Lymphocyte Ratio, Platelet Lymphocyte Ratio, Lymphocyte Monocyte Ratio, Positron Emission Tomography/Computed Tomography, 18FDG, Cancer Specific Survival, Overall Survival.

IINTRODUCTION:

Cancer remains one of the leading causes of mortality worldwide and is responsible for approximately 8.8 million deaths per year(*1*). Overall, it has been estimated that one in three people will develop cancer in their lifetime, and one in four will die from it (*2,3*). Indeed, in the UK alone it is estimated that 150,000 people die of cancer each year (*1,3*). Four cancers- lung, colorectal, breast and prostate account for approximately half of all new cases and deaths (*2*).

At a cellular level there are several traits of cancer that define its malignancy. These include genome instability, limitless replicative potential, self-sufficiency in growth signals, insensitivity to anti-growth signals, the ability to evade apoptosis, sustained angiogenesis, tissue invasion and metastasis, abnormal metabolic pathways, inflammation and evasion of the immune system (*4,5*). All these hallmarks create what is known as the tumour microenvironment (TME, (*4-6*)). The TME is composed of heterogeneous cell populations including tumour cells, immune cells, fibroblasts, adipocytes, blood vessels and the extracellular matrix. Therefore, there are interactions between malignant and non-transformed cells via a host of signalling molecules) (*7*). The tumour and its environment are constantly interacting and this is an integral part of the tumour physiology, structure and function. The relationship between the tumour and its environment is essential to promote tumour cell growth and the development of metastasis (*8*).

An important and long recognised characteristic of tumour cells is the dysregulated cellular energetics that results in the increased uptake of glucose(*9*). Warburg observed that tumour cells predominately produced adenosine 5′-triphosphate (ATP) via a high rate of glycolysis and consumption of glucose via the conversion of glucose to lactic acid. He recognised that this was inefficient for the tumour cell to produce ATP when compared to normal oxidative phosphorylation (*9,10*). Moreover, due to this anaerobic glycolysis and

lactic acid formation the TME would become acidic allowing for the de-differentiation of normal and malignant cells (*11*). Warburg hypothesised that this metabolic defect was the basis of tumour formation. In recent years it has been concluded that this metabolic defect is the result of genetic damage (39). Nevertheless, the impact of such dysregulated energetics of the tumour cell remains of considerable interest.

The TME is likely to have a direct impact on the innate immune response and activation of the systemic inflammatory response (SIR). This can be evidenced by increases in the circulating acute phase proteins such as C-Reactive Protein (CRP) and albumin and innate immune cells such as neutrophils and monocytes (*12*). These immune cells are also metabolically active requiring large amounts of glucose.

The prognostic value of the C-reactive protein, albumin and neutrophil counts in cancer has been well established in observational studies (*13,14*). In the last 15 years there has been a movement towards the use of combined prognostic scores such as the GPS/mGPS (C-reactive protein and albumin) and ratios such as the NLR (neutrophils and lymphocytes) to standardise and maximise prognostic value (*15,16*).

Therefore, it is of interest that imaging studies of the tumour have become an important element in the evaluation of detecting, staging and management of patients with cancer (*17*). Positron Emission Tomography (PET) is an established nuclear imaging technique based on the uptake of glucose that can examine the metabolism of tumours. However, PET provides relatively poor anatomical information whereas CT is commonly used in the initial diagnosis and staging of cancers.

The recent routine clinical combination of PET and CT gives anatomic information with associated assessment of tumour physiological activity (*18*). This provides better identification of metabolically active lesions improving the diagnostic accuracy and localisation of both the primary and metastatic lesions. In the oncological setting the tracer

^{18}F-2-fluoro-2-deoxy-D-glucose (18FDG) is commonly used due to its longer half-life which aids in transportation and clinical application (*19*). However, a disadvantage of this tracer is that it is not tumour cell specific, and can accumulate where there are metabolically active cells such as immune cells. For example, it is recognised to accumulate in bone marrow, presumably due to formation of metabolically active immune cells. This additional variability that can occur with uptake parameters such as the SUV (which depends on appropriate calibration and reconstruction methods with inter-site variability, and dependence on lesion or organ segmentation) has resulted in normalising uptake to other metabolically active tissues. Interestingly, an elevated bone marrow to liver ratio has been reported to have prognostic value in a variety of common solid tumours and an increased cytokine load due to malignancy (*20*).

Based on the above, it is hypothesised that glucose metabolism in both tumour and host inflammatory responses are related. This present review is timely given the rapidly expanding role of immune therapies (e.g. immune checkpoint inhibition and adoptive T-cell therapy) to treat patients with metastatic cancers. Therefore, the aim of this study was to carry out a systematic review of the relationship between tumour and host inflammatory glucose metabolism using PETCT. A better understanding of these processes would be useful to inform therapeutic strategies for patients with cancer.

METHODS:

This systematic review of published literature was undertaken according to a pre-defined protocol described in the PRISMA-P statement. The primary outcome of interest of this systematic review was the relationship between tumour and host inflammatory glucose metabolism specifically using PETCT imaging in patients with cancer. The secondary outcome of interest of this systematic review was the association between tumour and host inflammatory glucose metabolism as measured by PETCT imaging and survival in patients with cancer.

Studies were identified via a literature search of the electronic databases the US National Library of Medicine, the Excerpta Medica database and the Cochrane Database of Systematic Reviews between 1984 and 2018 using the following keywords: cancer, malignancy, metastasis, inflammation, glucose, positron, CT and PETCT (last search update on 31st March 2018).

To be eligible for inclusion, studies had to meet the following criteria. (a) Patients with cancer (b) PETCT analysis the imaging modality used (c) Tumour (T) and/or bone marrow (BM) activity measured by either SUVmax, SUVmean or the bone marrow to liver ratio (BLR: mean BMSUV to mean Liver SUV ratio) (d) markers of the systemic inflammatory response in the form of acute phase proteins (CRP and albumin) or components of the differential blood cell counts (neutrophils, leukocytes, monocytes and platelets) and their composite scores such as the modified Glasgow Prognostic Scores (mGPS), Platelet Lymphocyte Ratio (PLR) and NLR. Exclusion criteria included (a) studies not carried out in patients with cancer (b) studies not using PETCT as the main imaging modality (c) studies not assessing tumour and bone marrow activity and (d) studies not including measurement of the SIR.

On completion of the online search, the title and abstract of each identified study was examined for relevance. Studies not in cancer patients, studies not available in English and those published in abstract form only were excluded. Where there were multiple publications from the same cohort the most recent paper was included. Full texts were obtained for all studies deemed potentially relevant. Once further exclusions outlined above were carried out, the bibliographies of all included articles were subsequently hand searched to identify any additional studies. Due to the small number of studies and the heterogeneity of tumour type and tumour/bone marrow activity assessment, meta-analysis was not carried out.

RESULTS:

Study Selection Process

The study selection process is summarised in Figure 1. Initial search strategy identified 207 articles whose titles and abstracts were reviewed. Articles were excluded if they had not been carried out in humans (n=64), no full texts were available (n=12), those that were a systematic review/meta-analysis (n=32) and those not published in English (n=6). This led to a review of the full text of 93 articles. A further 83 articles were excluded as there was no direct comparison between the SIR and PET-CT output. The remaining 10 articles had their bibliographies reviewed in a systematic manner. This identified a further 2 articles to be included in the final analysis leading to final figure of 12 articles considered in the present systematic review (*20-31*).

Overall Analysis

The eleven included studies contained a total of 2,468 patients with the number of patients included in individual studies varying from 32 to 1,034 (Supplementary File). There was a wide variety in cancer anatomical locations including lung (n=4), oral (n=3), colorectal (n=2), gastric (n=1), head and neck (n=1) and multiple anatomical locations (n=1). Geographically studies were from Korea (n=5), China (n=2), Belgium (n=1), Taiwan (n=1), Canada (n-1), Japan (n=1) and the UK (n=1).

The majority of studies showed a direct relationship between the host systemic inflammatory response and the indices of FDG accumulation as measured by BLR (n=5), BMSUVmax (n=4), TSUVmax (n=4), BMSUVmean (n=2), NSUVmax (n=2), SUVpeak (n=1), MRV (n=1) and TLG (n=1). In addition, the majority of studies showed a direct

relationship between survival and indices of FDG accumulation BLR (n=3), TSUVmax (n=2), BMSUVmean (n=2), BMSUVmax (n=1), NSUVmax (n=1) and TLG (n=1).

All studies used the radioisotope 18F-FDG. There was some variation in the type of scanners used with the most common scanners being Siemens (n=5) and General Electric (n=4). In all studies patients were required to fast for minimum of 4-6 hours prior to the PET-CT study protocol being initiated and fasting blood glucose levels were measured prior to the administration of 18F-FDG. The majority of studies had a blood glucose threshold level of < 150.0 mg/dL for the injection of the radioisotope. There was some variation in the activity of 18F-FDG administered, however all studies used weight based protocols with administered activities ranging between 230-555 MBq. PET acquisition in the majority of studies was from base of skull to proximal thigh, using 6 – 8 bed positions, acquired 60 minutes post FDG administration. All reconstructions involved CT attenuation correction and iterative reconstruction algorithms specific to the camera manufacturer's software. Regions of interest (ROI) were either drawn freehand, using a minimum SUV cut off or by using isocontour software. The SUV parameters measured varied slightly although in general the maximum and mean SUV values were measured for the primary tumour (TSUVmax, TSUVmean), nodal disease (NSUVmax, NSUVmean) and bone marrow (BMSUVmax, BMSUVmean). The bone marrow to liver ratio (BLR) was defined using SUVmean measurements in the bone marrow, obtained mainly from vertebral bodies, and SUVmean from an ROI in the right lobe of liver.

The majority of studies focused on patients with stage I-III disease who were treated with surgical resection with or without adjuvant chemoradiotherapy (n=8). In those studies

where surgery was not the mainstay of treatment only one study had a majority of metastatic disease (79.2%) (*24*). Two studies were in Ear Nose and Throat (ENT) cancers with the treatment of choice being concurrent chemoradiotherapy and definitive radiotherapy (*24,26*). One study was in patients with advanced Non Small Cell Lung Cancer (NSCLC) not amenable to surgical resection and one study was in multiple cancer types again not amenable to surgical resection (*20,28*).

The majority of studies use singular markers of the systemic inflammatory response including the WCC (n=9), CRP (n=7), haemoglobin (n=4), albumin (n=3), neutrophils (n=2), platelets (n=2), lymphocytes (n=1) and monocytes (n=1). In addition composite ratios and scores were used in several studies including the NLR (n=7), PLR (n=5) and mGPS (n=1). Multiple markers of the systemic inflammatory response were used however there was considerable heterogeneity in the specific markers used.

Therefore, a meta-analysis could not be meaningfully carried out due to the heterogeneity of tumour stage, tumour type and markers of the SIR.

Relationship Between Tumour Glucose Metabolism using TSUVmax/mean, BMSUVmax/mean and BLR and Host Inflammatory Responses

As can be seen in the supplementary file the majority of studies would appear to be significantly association between activation of the SIR and increased tumour, bone marrow and nodal uptake in PET-CT. In particular, the largest study (n=1034) included in this review reported such a relationship (*25*).

Jeong and colleagues compared the prognostic values of circulating blood cell-based parameters and tumour FDG uptake in patients with stage I NSCLC(*25*). In total 1034 patients were included in this study. They were all newly diagnosed with NSCLC and underwent PET-CT scanning as part of their preoperative workup prior to undergoing surgical resection (*25*). Biochemical and haematological measurements in the form of WCC, neutrophil, lymphocyte and platelet counts were taken(*25*). These were then used to calculate the composite ratios NLR and PLR. PET-CT scan analysis focused on tumour FDG uptake (*25*).

The median age of the included patients was 61.6 years and 58.9% were male with 50.6% having never smoked(*25*). The majority of patients had adenocarcinomas (76.7%) and were treated by lobectomy (87.1%) (*25*). There were 144 recurrences and the median follow up was 29.5 months (*25*). Patients with a high TSUVmax had significantly higher WCC ($p<0.001$), neutrophil ($p<0.001$) and lymphocyte counts ($p=0.002$), and a greater NLR ($p=0.016$) (*25*). On univariate Cox regression analysis, WCC ($p=0.028$), TSUVmax ($p<0.001$), age ($p<0.001$), gender ($p=0.003$), smoking ($p=0.002$), cell type ($p=0.001$), and TNM stage ($p<0.001$) were significantly associated with disease specific survival (*25*). On multivariate analysis, TSUVmax (HR: 2.22 95% CI, 1.52–3.25; $p<0.001$), tumour stage (HR: 2.11 95% CI, 1.47–3.01; $p<0.001$), and old age (HR:1.03 95% CI, 1.01–1.05; $p=0.002$) remained independently prognostic in terms of disease specific survival (*25*).

DISCUSSION

The results of the present systematic review showed that, in the majority of studies, there was a direct relationship between the tumour and bone marrow glucose uptake and host systemic inflammatory responses in patients with common solid tumours.

Both tumour and nodal glucose uptake and bone marrow glucose uptake were associated with poor outcome in these patients. Although bone marrow FDG accumulation may mainly reflect inflammatory responses, tumour and nodal FDG accumulation reflect the malignant grade of the tumour cells in addition to the inflammatory responses. Therefore, it may be that the nature of their associations with survival will be different.

Taken together the present review provides new insight into the interaction between tumour and host. This may suggest new approaches to more optimal therapeutic targeting and monitoring strategies for patients with cancer.

The basis of the relationship between tumour glucose uptake and markers of the systemic inflammatory response is not clear. The importance of the tumour microenvironment is increasingly appreciated. In addition to the tumour cells themselves stromal cells and inflammatory cells are now recognised to play a role in growth and progression of cancer. The predominant cells in the tumour stroma are the cancer-associated fibroblasts (CAFs) that have been shown to promote tumour progression and invasion through the production of growth factors, cytokines and metabolites and stimulate blood vessel formation (*32*). Such stromal cell activity is intimately linked to inflammatory cell activity and macrophages contribute to tumour progression and spread by the promotion of genetic instability, protection and nurturing of cancer stem cells, promotion of metastatic spread and the downregulation of the protective T-cell driven adaptive immune response (*33-35*). In turn, such macrophage activity appears to be dependent on the tumour stage, tissue involvement and microbiota (*33*). The macrophage influence on tumour activity can be pro-

inflammatory and tumour growth promoting via the classical M1 pathway commonly upregulated by the inflammatory cytokines TNF-α and IL-6 (*36*). As well as anti-inflammatory and tumour growth reducing via the alternative M2 pathway commonly unpregulated by the anti-inflammatory cytokines IL-4 and IL-10 (*36*).

The importance of neutrophil activity and infiltrate in cancer progression and metastasis has become an increasingly recognised prognostic domain. Neutrophil activity has been shown to increase tumour progression by facilitating and encouraging angiogenesis (*37*). Neutrophil activity has also been implicated in potentiating tumour growth through the activation of specific inflammatory cytokines particularly IL-1 and IL-6 and via amino acid depletion (*37*) and promotes angiogenesis and the metastatic potential of cancer (*37*). Neutrophils have also been shown to direct cancer cell growth towards endothelial cells which can lead to increased haematological spread promoting distant metastasis (*37*). Indeed in the pre-metastatic state in patients with advanced cancer neutrophil clusters or localised build-ups in distant organs has been shown to be predictive of eventual metastatic spread (*37*).

Finally, it has also been postulated that cytokines produced by the tumour/stroma complex can lead to marrow mesenchymal cell recruitment as a thus providing a potential explanation for increased marrow activation seen in the present review (*35*).

However, there is recognised uptake of 18FDG by both tumour and inflammatory cells and that the TME consists of both tumour and inflammatory cells (*38*). Therefore, part of the glucose uptake into the tumour may be due to the infiltration of inflammatory cells. Indeed, Rosenberg and colleagues proposed caution when analysing PETCT scans as the marrow hypermetabolism shown may be due to inflammation and not necessarily where the tumour cells are located (*39*).

While bone marrow mesenchymal stem cells, monocyte or platelet progenitor cells are unregulated during the response to active malignancy an elevation of neutrophils which is quantitatively the most important cell type has been consistently seen in patients with active cancer as shown by the prognostic strength of neutrophils singularly and NLR (*15,40*)."

However, confirmation of this hypothesis will require careful histological examination of the areas of both tumour and bone marrow increased signal uptake." Irrespective, it is clear that both tumour and inflammatory cells display signs of the "Warburg effect" and it may be that both contribute to the increased lactate dehydrogenase and its prognostic value observed in patients with cancer (*41,42*).

In the present review it was confirmed that there was a relationship between tumour and bone marrow glucose uptake and poor outcome in patients with cancer confirming its clinical utility. Given that two recent meta-analysis have established the prognostic strength of both singular and combined markers of the systemic inflammatory response in both operable and inoperable disease across multiple cancer types (*15,16*) it remains to be determined whether the prognostic value of tumour and bone marrow glucose uptake is determined by the systemic inflammatory response or vice versa.

While the majority of the above studies used singular markers of the systemic inflammatory response these have now been surpassed by the use of composite ratios and cumulative scores (*15,16*). Furthermore in a recent study in operable colon cancer Dolan and co-workers showed that both composite ratios and cumulative scores had prognostic value, independent of TNM stage (*40*). However, cumulative scores, based on normal reference ranges, are simpler and more consistent for clinical use and should be used in future research to investigate the association between FDG-PET imaging and host inflammatory responses"

The importance of the relationship between tumour and bone marrow glucose uptake and the systemic inflammatory response is of more than academic interest particularly

in the era of immunomodulatory therapy for patients with advanced cancer. In particular, modulation of the innate and adaptive immune responses will shed new light on the nature of this relationship (*43*). Furthermore, while there was some heterogeneity in the results, there was a relationship between tumour and bone marrow glucose uptake and poor outcomes in five studies including 1,525 patients.

To our knowledge this is the first systematic review to examine the relationship between tumour glucose metabolism using PETCT imaging and host inflammatory responses. From the review there appeared to be a direct relationship between the tumour and bone marrow glucose uptake and host systemic inflammatory responses in patients with common solid tumours. Furthermore, there was a relationship between tumour and bone marrow glucose uptake and poor outcome in these patients.

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Figure1. A PRISMA Flowchart demonstrating study selection process.