Is it time to incorporate fludeoxyglucose PET/CT markers into sarcoma prediction models?

"...PET/CT can provide precise, reproducible information on tumor size and multifocality, and is strongly correlated with the histopathological features that make up the Federation of Cancer Centers Sarcoma Group grading system."

KEYWORDS: biomarker ▪ FDG PET/CT ▪ necrosis ▪ prediction models ▪ sarcoma ▪ tumor grading

Rajan Rakheja
*Author for correspondence:
Division of Nuclear Medicine, Royal University Hospital, University of Saskatchewan, Saskatoon, SK, Canada
rajan.rakheja@gmail.com*

Stephan Probst
Division of Nuclear Medicine, Jewish General Hospital, Montreal, QC, Canada

Sarcomas are relatively rare primary malignancies that originate from the embryonic mesoderm and are responsible for less than 1% of adult cancers, but comprise approximately 6% of childhood malignancies [1]. Despite aggressive therapy, including surgery, adjuvant chemotherapy and radiotherapy, sarcoma patients' prognosis remains guarded and overall survival has not improved substantially over the past few decades; 40% of patients with high-grade lesions will die from metastatic disease [1].

At initial histopathologic diagnosis, sarcoma grading is a fundamental step in patient evaluation and plays a prominent role in overall staging. As recognized by WHO, there are two principle grading systems – the National Cancer Institute and the French Federation of Cancer Centers Sarcoma Group (FNCLCC) [2]. The more widely-used FNCLCC grade is based on three parameters: tumor differentiation, mitotic activity and necrosis. Each of these parameters receives a score: differentiation (1–3), mitotic activity (1–3) and necrosis (0–2). The sum of the scores generates a grade: grade 1 is a score of 2–3, grade 2 is 4–5 and grade 3 is 6–8.

Sarcomas are extremely heterogeneous tumors, which often contain high-grade components, in addition to lower-grade areas. Frequently, sarcomas show intratumoral necrosis, further complicating histopathological assessment. As a result of this heterogeneity, difficulty arises in accurately grading sarcomas as the assessment becomes dependent on which part of the sarcoma was biopsied and/or selected for histologic examination by the pathologist. Significant pathologist interobserver variability exists when determining the histological sarcoma type, presence of necrosis and quantifying mitotic activity [3]. Given the importance of accurately determining tumor grade – and subsequently prognosis and treatment – there is much need for metabolic imaging modalities to provide synergistic, reproducible and nonoperator-dependent variables for this assessment.

^{18}F-fludeoxyglucose (FDG) PET/CT is sensitive and specific in the TNM staging and restaging of sarcomas [4,5]. In addition, the metabolic information provided by FDG PET/CT correlates positively with the individual FNCLCC system markers and overall sum. Several studies have shown that FDG PET/CT correlates with overall tumor grade; a meta-analysis of over 440 patients observed that a large majority of intermediate- and high-grade sarcomas can be correctly identified using metabolic FDG PET quantification, using a cutoff of SUV_{max} of 2.0 or more [6]. Similarly, Eary *et al.* accurately employed FDG PET/CT in 70 patients to differentiate between the histologic grades of the National Cancer Institute grading system. Furthermore, in a histopathological review of 136 soft tissue and osseous sarcomas, it was shown that SUV_{max} correlated positively with degree of tumor necrosis [7]. Several studies have demonstrated SUV_{max} correlates with mitotic count; Folpe *et al.* compared SUV_{max} of 89 sarcomas with mitotic count and found a strong correlation between the two variables [8].

Given that the metabolic data, specifically SUV_{max}, from FDG PET correlates so well with the sarcoma FNCLCC system components, the authors wonder why PET/CT has not been more widely incorporated into sarcoma prediction models. Moreover, PET/CT information is often available well before final histopathological assessment as it is commonly ordered during initial staging. The prognostic value of FDG PET/CT for malignancies has been well described in the literature; PET/CT results correlate with prognosis in lung cancer [9,10],

Future Medicine part of fsg

esophageal cancer [11], anal cancer [12] and in sarcomas [13]. These results strongly support the use of PET/CT in prognostic scoring models.

A standard prognostic tool is indispensable in the evaluation of rare tumors, such as sarcomas and for managing therapy for individual patients. Treatment regimens are driven not only by sarcoma subtype and grade, but also by prediction models to assess how well a patient will fare. For example, a patient who is at high mortality risk due to their sarcoma, is a prime candidate for more aggressive treatment. One of the most widely used sarcoma prediction models is the Memorial Sloan-Kettering Cancer Center Sarcoma Nomogram [101]. The Sarcoma Nomogram allows for integration of several prognostic variables to aid the multidisciplinary team in a complex decision-making process.

> "…the authors envision a future multidisciplinary sarcoma tumor board meeting where a presurgery evaluation of prognosis is undertaken…"

The Memorial Sloan-Kettering Cancer Center Sarcoma Nomogram prognostic model utilizes the following information: sarcoma subtype, patient age, tumor size and depth, disease site, histology, and tumor grade. The model estimates a specific probability of disease-specific mortality for the 12-year period following surgery. The Memorial Sloan-Kettering Cancer Center Sarcoma Nomogram was validated in an analysis with more than 1000 patients, which confirmed that it provided accurate survival predictions [14]. Since FDG PET/CT can provide accurate and rapid information about the tumor size, depth and site, and shows strong correlation with the tumor grade, it appears logical that this information should be included in a prediction model for sarcomas. Furthermore, FDG PET provides this data in a timely fashion, with excellent interobserver agreement and does not suffer from the sampling biases of histopathology in highly heterogeneous sarcomas.

Newer sarcoma prediction models, such as the one specifically designed for retroperitoneal soft tissue sarcomas, incorporate other prognostic features including tumor size, FNCLCC grade, histologic subtype and multifocality [15]. Again, PET/CT can provide precise, reproducible information on tumor size and multifocality, and is strongly correlated with the histopathological features that make up the FNCLCC grading system [7,8,16].

Given that FDG PET/CT correlates with several of these prediction model variables and with mortality [13], the authors hope to see a future large prospective study to design a sarcoma prediction model that incorporates the readily available and reproducible anatomic and metabolic data from FDG PET/CT. PET/CT is widely available in North America and Europe in major oncologic centers and is the standard of care for sarcoma patients where available – cost and accessibility should not be barriers to implementation. In fact, the authors envision a future multidisciplinary sarcoma tumor board meeting where a presurgery evaluation of prognosis is undertaken; FDG PET/CT would provide an estimate of tumor size, site, heterogeneity, multifocality and tumor necrosis and grade, thus allowing a rapid initial evaluation of sarcoma prognosis – even guiding surgical technique. Moreover, in cases where there was pathological interobserver disagreement or where classification using histopathologic criteria alone was suboptimal, FDG PET data could be complementary and possibly guide additional biopsy to an area that would resolve the ambiguity.

Future perspective

The future of sarcoma molecular imaging is bright with the evolution of hybrid PET/MRI, which has the ability to provide superior anatomical soft tissue resolution as compared with PET/CT, in addition to the metabolic data of PET. Also, new PET tracers such as 3′-deoxy-3′-[^{18}F] fluorothymidine, which has shown a lot of early promise in tumor node metastasis staging and noninvasive grading, and [^{18}F] fluoromisonidazole, which can be used to asses tumor hypoxia and grade, are actively being investigated. These advances in the field, although not ready for routine clinical use at the time of writing, are exciting prospects that likely represent the future of disease management.

Conclusion

In conclusion, we believe that it is time to investigate an FDG PET/CT-based prediction model in sarcoma patients. This modality is an extremely detailed, available, reproducible, noninvasive imaging technique that can clearly contribute valuable information in determining prognosis in this rare, heterogeneous and highly lethal group of tumors. We hope to see a large trial undertaken within the next few years, to advance care for these patients.

References

1   Iagaru A, Chawla S, Menendez L, Conti PS. 18F-FDG PET and PET/CT for detection of pulmonary metastases from musculoskeletal sarcomas. *Nucl. Med. Comm.* 27, 795–802 (2006).

2   Shives TC. Biopsy of soft-tissue tumors. *Clin. Orthop. Relat. Res.* 289, 32–35 (1993).

3   Presant CA, Russell WO, Alexander RW, Fu YS. Soft-tissue and bone sarcoma histopathology peer review: the frequency of disagreement in diagnosis and the need for second pathology opinions – the Southeastern Cancer Study Group experience. *J. Clin. Oncol.* 4, 1658–1661 (1986).

4   Kern KA, Brunetti A, Norton JA *et al.* Metabolic imaging of human extremity musculoskeletal tumors by PET. *J. Nucl. Med.* 29, 181–186 (1988).

5   Charest M, Hickeson M, Lisbona R *et al.* FDG PET/CT imaging in primary osseous and soft tissue sarcomas: a retrospective review of 212 cases. *Eur. J. Nucl. Med. Mol. Imaging* 36(12), 1944–1951 (2009).

6   Ioannidis JP, Lau J. 18F-FDG PET for the diagnosis and grading of soft-tissue sarcoma: a metaanalysis. *J. Nucl. Med.* 44, 717–724 (2003).

7   Rakheja R, Makis W, Skamene S *et al.* Correlating metabolic activity on 18F-FDG PET/CT with histopathologic characteristics of osseous and soft-tissue sarcomas: a retrospective review of 136 patients. *AJR Am. J. Roentgenol.* 198 (6), 1409–1416 (2012).

8   Folpe AL, Lyles RH, Sprouse JT, Conrad EU 3rd, Eary JF. (F-18) fluorodeoxyglucose positron emission tomography as a predictor of pathologic grade and other prognostic variables in bone and soft tissue sarcoma. *Clin. Cancer Res.* 6, 1279–1287 (2000).

9   Higashi K, Ueda Y, Arisaka Y *et al.* 18-F-FDG uptake as a biological prognostic factor for recurrence in patients with surgically resected non-small cell lung cancer. *J. Nucl. Med.* 43(1), 39–45 (2002).

10   Ahuja V, Coleman RE, Herndon J, Patz EF Jr. The prognostic significance of fluorodeoxyglucose positron emission tomography imaging for patients with nonsmall cell lung carcinoma. *Cancer* 83, 918–924 (1998).

11   Rizk NP, Tang L, Adusumilli PS *et al.* Predictive value of initial PET-SUV$_{max}$ in patients with locally advanced esophageal and gastroesophageal junction adenocarcinoma. *J. Thorac. Oncol.* 4, 875–879 (2009).

12   Kidd EA, Dehdashti F, Siegel BA, Grigsby PW. Anal cancer maximum F-18 fluorodeoxyglucose uptake on positron emission tomography is correlated with prognosis. *Radiother. Oncol.* 95, 288–291 (2010).

13   Schwarzbach MH, Hinz U, Dimitrakopoulou-Strauss A *et al.* Prognostic significance of preoperative [18-F] fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging in patients with resectable soft tissue sarcomas. *Ann. Surg.* 241, 286–294 (2005).

14   Eilber FC, Brennan MF, Eilber FR, Dry SM, Singer S, Kattan MW. Validation of the postoperative nomogram for 12-year sarcoma-specific mortality. *Cancer* 101(10), 2270–2275 (2004).

15   Gronchi A, Miceli R, Shurell E *et al.* Outcome prediction in primary resected retroperitoneal soft tissue sarcoma: histology-specific overall survival and disease-free survival nomograms built on major sarcoma center data sets. *J. Clin. Oncol.* 31(13), 1649–1655 (2013).

16   Costa J, Wesley RA, Glatstein E, Rosenberg SA. The grading of soft tissue sarcomas: results of a clinicohistopathologic correlation in a series of 163 cases. *Cancer* 53, 530–541 (1984).

■ Website

101   Memorial Sloan-Kettering Cancer Center. Sarcoma Nomogram: post-surgery. http://nomograms.mskcc.org/Sarcoma/PostSurgery.aspx