

## Opinion

## Pre-therapeutic (18) F-fluoro-2-deoxyglucose Positron Emission Tomography (18F-FDG PET) in Cervix Cancer: Is it a Reliable and Independent Prognostic Factor for Survival?

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There has been an ongoing quest to identify new prognostic factors in cervix cancer patients in addition to FIGO stage, tumour volume and nodal involvement in order to tailor individualized patient management and improve survival.

Positron Emission Tomography (PET) - Computer Tomography (CT) with 18-F-2-fluoro-2-deoxyglucose (FDG) has been shown to be invaluable in the diagnosis and staging of cervix cancers as well as many other malignancies. PET has demonstrated the ability to detect neoplastic involvement in lymph nodes of normal or borderline size and the advent of hybrid PET-CT has further improved its anatomic localisation of lesions of interest [1]. Several studies have demonstrated that FDG-PET is superior to conventional imaging methods for detecting metastatic disease especially those in the lymph nodes and is helpful in staging, restaging and treatment planning of patients with cervix cancer [2-4].

In addition to its efficacy in assessing nodal and metastatic disease, FDG-PET/CT is thought to have a potential role as a prognostic factor [5].

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### Standardized Uptake Value (SUV)

FDG uptake is commonly expressed as the Standardized Uptake Value (SUV). SUV is a semi quantitative value defined as the tissue concentration of FDG in the region of interest (kBq/ml) divided by the activity injected per gram body weight (kBq/g). SUVmax is defined as follows: maximum pixel value in the tumour (kBq/ml)/ [injected dose (kBq)/ patient weight (g)].

FDG uptake is dependent on glucose utilization by cells and may correlate with tumour proliferation, inflammation and arguably tumour aggressiveness [6]. SUVmax of the primary tumour has been suggested to be predictive of Lymph Node (LN) involvement, treatment response and overall survival [5]. Differential behavior to SUV has been investigated in many types of cancer, including lymphoma, Non-Small Cell Lung Cancer (NSCLC), esophageal cancer, and head and neck cancer [7,8]. For NSCLC in particular, FDG uptake has been shown to be significantly different for adenocarcinoma versus squamous cell carcinoma and for well-differentiated versus poorly differentiated tumors [9]. On the other hand, some types of aggressive cancer such as clear cell or certain subtypes of sarcomas may show relatively low FDG uptake.

The exact mechanism of differential FDG uptake by tumour is unclear. There appears to be a correlation between FDG uptake and Glut-1 expression, which has led to research into glucose transporter gene expression [10]. In breast cancer patients, Bos et al., [11] found a correlation between FDG uptake and Glut-1 expression, mitotic index, amount of necrosis, tumor cell volume, and micro vessel density. In NSCLC patients, increased FDG uptake correlated with expression of Hypoxia-inducible Factor 1-alpha (HIF-1a) and Glut-1 expression [12]. Similar correlation between higher SUV and Glut-1 expression [13] as well as Glut-1 overexpression and tumour grade [14] was found in cervix cancers patients. In contrast, no correlation was found between Glut-1 and Glut-3 expression and tumour differentiation or indeed SUVmax in oral Squamous Cell Carcinoma (SCC) [15].

### The Role of SUV in Prognosticating Cervix Cancer

There have been several studies that suggest association of increased SUV with worse outcome [16,17]. However, the so called "best cut-off" value of the SUVmax as well as the method of obtaining it has not been consistent in the literature. Kidd et al., [5] showed SUVmax using cut-off values at quartiles had no co-relation of SUV with tumour volume. However, higher SUV was associated with poor Overall Survival (OS) and persistent disease at the primary site. Onal et al., [18], showed that SUVmax of the primary tumour >15.6 and the presence of lymph node metastasis were independent prognostic factors for OS. In this study, SUVmax was investigated using a "best cut-off" value using Receiver Operating Characteristic (ROC) curve analysis and a higher value was found to be associated with poor prognosis. Inter-relation between SUVmax of the pelvic lymph nodes, tumour volume of the primary and outcomes were investigated by Kidd et al., using the logistic likelihood ratio test [19]. They showed SUVmax of the Pelvic Nodes (SUVPLN) did not strongly relate to either the size of pelvic nodes or to the SUVmax of

the primary tumour. However an elevated SUVPLN was related to the persistent disease in pelvis.

## Currently Known Prognostic Factors in Cervix Cancer

Traditional prognostic factors in cervix cancer include FIGO stage and nodal status. FIGO staging of cervix cancer first published in 1929 (<http://www.figo.org/>) was originally based on the extent of the local tumour spread in the tissue compartments. This was useful in assessing the surgical resectability of cervix cancer. The resulting histo-pathological findings then could be used for deciding on additional therapies in the event surgery was not deemed sufficient for cure. This worked very well in the early stages of mostly node negative cervix cancer patients where a Gynecologic-Oncology Group (GOG) score [20] of <120 or >120 could be used to assign patients to no further treatment or for adjuvant pelvic radiotherapy. This resulted in about 40% reduction in mortality in patients who scored >120 and were treated with adjuvant radiotherapy.

However, in advanced stage disease or in patients with a large volume disease the prognostication based of compartmental spread of tumour remain inadequate. Realizing the importance of tumour volume FIGO stage 1 and 2A was again modified to subdivide stage 1B into 1B1, 1B2 and 2A into 2A1 and 2A2 using 4 cm clinical tumour diameter as a cutoff point.

Clinical estimation of tumour size and hence volume was highly subjective and correlated very poorly with histological findings. CT scanning was only marginally better in estimation of tumour volume, although it could easily detect enlarged metastatic lymph nodes. MRI provided a more accurate measure of tumour volume that co-related with histological measurements well [21]. Subsequently, tumour volume was used as a dichotomized value (13 cc) in selecting treatment modalities in small operable tumours [22] or in prognostication of treatment outcome in larger (50 cc) tumours [23]. MRI-obtained tumour volume was assessed for prognostic significance in a multivariable analysis in 179 patients treated with curative intent, and it was found to be a continuous variable further influenced by tumour infiltrating in the uterine corpus [24] or the presence of nodal metastasis [25].

In advanced cervix cancer patients where surgery is inappropriate and in order to assess the known prognostic factors by non-invasive methods, MRI to assess the local spread of tumour as well as volume and the use of PET scans to assess the metastatic lymph nodes and their station were invaluable. It has been shown that five year survival rates in patients with corpus non-invasive tumour was 77% and those with corpus invasion was 41% [24]. Those without the lymph node metastasis and with lymph node metastasis the 5 year survival was 70% and 48% respectively [25]. Those with lymph node metastasis limited to pelvis was 57% and where it extended to involve para-aortic nodes the survival declined to 32-26% [26,27].

Based on the current knowledge of prognostic markers in cervix cancer, there is no one all-encompassing prognostic marker that can put a single numerical value or a series of discrete values predicting an outcome better than the combination of MRI volume, (analyzed as a continuous variable) and nodal status on PET-CT imaging as a dichotomized value such as lymph node metastasis present/not present and if present, the echelon of lymph node involved.

## Where Does the SUVmax Fit in This Prognostic Matrix?

It may be true that a more metabolically active tumour may have a higher proliferative capacity, have the potential of acquiring tumour volume at a higher rate and possibly be more locally aggressive compared to a less metabolically active tumour. However, there are host-related mechanisms, which are independent of tumour metabolism and not fully understood, that influence tumour spread, metastasis and survival.

In order to survive and metastasize, it is hypothesized that tumour cells from the primary site would be required to come in contact with the terminal lymphatics, survive in the lymphatic space, invade lymph nodes where they would need to evade the host immune response, continue to proliferate and be selected for clonal expansion to replace lymph nodes with metastases. These cells also need to come in contact with intertissular lymphatic-venous anastomoses [28], pass in to circulation, survive and find a suitable tissue to colonize and form distant metastases.

When a matrix of invasiveness and local growth is observed by MRI and the distribution of viable tumour colonies is detected by PET imaging, a complete snap shot of tumour and host interaction is assessable and accurate prediction of prognosis becomes possible. A single value, (or a range of values simply based on metabolic capacity of the primary tumour devoid of any host interaction parameters), such as SUVmax alone, would only enable one to know the potential of the tumour to exhibit a more or less aggressive behavior, rather than actually predict the likelihood of recurrence. For example, in uterine cancers, it is known that serous and clear cell histologies have a poorer prognosis compared to endometrioid histologies. However, the overall prognosis is further modified by other prognostic factors, such as the presence or absence of Lymphovascular Space Invasion (LVSI) or lymph node metastasis. In fact, patients with clear cell and endometrioid histologies that are lymph node negative and do not have LVSI, were both found to have <8% recurrence rates [29]. However LVSI positive endometrioid histology will still have worse prognosis than LVSI and node negative clear cell or serous cancers of uterus.

Therefore, just as “bad” histology on its own is not sufficient to predict prognosis, we believe that an increased SUVmax (a sign of increased metabolic activity) in isolation is likewise insufficient as a reliable predictor of treatment outcome.

In a study by Kidd et al., [30] a PET-based nomogram was used which included tumour volume, SUVmax of primary tumour and presence of and level of nodal involvement. The authors found that the most significant poor prognostic factor was the detection of lymph node metastasis by PET imaging and the level of nodes, rather than their SUVmax. SUVmax value was only marginally better than tumour volume for predicting Relapse Free Survival (RFS). The HR for OS in locally advance cervix cancer was 0.6, 1.12, 1.40 and 3.24 in node negative, pelvic, common iliac and para-aortic node positive patients respectively [25], in comparison, HR for OS was of 1.009 for SUVmax of >14 for primary tumour [30]. Perhaps the prognostic significance of SUVmax of the primary tumour could be better explored in PET node negative patients for it to have a practical application.

We believe several aspects related to SUVmax need to be explored before it could become a practical and reproducible prognostic parameter useful in the management of cervix cancer patients.

- Is SUVmax a continuous variable or it can be subdivided in quartiles or even dichotomized?
- What is the best way of integrating the SUVmax of Lymph Nodes (SUVLN) in the presence of nodal metastases in the overall matrix of a SUVmax based prognostic tool?
- Are there different implications on the interpretation of the prognostic potential of SUVmax (primary tumour) in node negative and node positive patients? Should there be separate SUVmax based prognostic tools?
- Since SUVmax is measured in relation to background uptake, for example, in liver, where this background uptake could vary from patient to patient, is there a need for a universal correction factor?

We have more than 300 patients of cervix cancer treated with curative intent between 2002 and 2010 who underwent pretreatment

The initial disease parameters upon diagnosis, related known prognostic factors, as well as subsequent relapse time line, the site of relapses, disease status and at last follow-up is shown in table 1. The pre-treatment SUVmax of the primary tumour in relation to their other parameters and subsequent outcome is shown. In this cohort of patients, there were no primary site or pelvic nodal failures. Only 1 out of 7 node negative patients have relapsed, of whom the pre-treatment SUVmax of primary tumour ranged from 4.2 - 17.5. The one who failed had SUVmax 14.4. Out of the 9 node positive patients (SUVmax ranged from 6.7 - 46), 4 have relapsed (SUVmax were 9.3, 21.9, 26.7 and 46 respectively). It is interesting to note that patient No 8 who had a small tumour with nodal involvement involving upper PA node, had SUVmax of 9.3, relapsed in supraclavicular nodes and lung and mediastinum and received high dose palliative radiotherapy to these sites is alive with disease present only in lung at >6 years since the initial diagnosis of her cervix cancer.

Patient	FIGO	SUV	MRIVol	No + nodes	Highest Involved node	SUV Max	Relapse & Follow up		
	Stage	max				(LN)			
		(Primary)					Site	Status	Days Survived
1*	2A	4.2	1	0				Dead (other)	393
2*	1B	2.5	4	0				Alive	2426
3*	2B	6.7	15	0				Alive	2325
4*	3A	9.1		0				Alive	2244
5#	1B	6.7	1	2	Inf PA	3.1		Alive	1384
6#	1B	10.6	6	4	Common Iliac	13		Alive	2014
7#	2A	24.4	6	4	Common Iliac	3.8		Alive	1568
8#	2A	9.3	27	4	upper PA	4.9		Alive	1842
9\$	1B	15.6	52	0				Dead (other)	805
10\$	2B	17.5	69	0				Alive	2041
11\$	1B	14.5	100	0			PA, D	Dead (tumour)	513
12@	3B	26.7	84	2	Pelvic	15.5	PA, SC, D	Dead (Tumour)	1079
13@	3B	21.9	201	2	Pelvic	10.7	D	Dead	1039
14@	2B	46	238	4	Common Iliac	33.5	D	Dead	1008
15@	2B	15.2	291	3	Inf PA	6.9		Alive	1658
16@	4A	19.2	293	4	Common Iliac	12.5		Alive	1464

**Table 1:** Patient and disease characteristics, SUVmax and subsequent follow up following definitive chemo-irradiation.

PA= Para Aortic; Inf = Inferior; SC = Supraclavicular; D = Distant; P = Primary; N = Node

\* = small primary, node negative; # = small primary, node positive; \$ = large primary, node negative; @ = large primary, node positive

PET and MRI studies. The details of the pretreatment assessment, histopathological data, treatment and follow-up have been prospectively collected and recorded in our institutional database. We are currently testing the hypothesis that there would be a trend of higher SUVmax with the lymph node metastases but survival will relate the level of nodal metastases and only in node negative patients SUVmax may have a significant prognostic role in stratifying patients over tumour volume and the FIGO stage of the disease.

As a pilot study to test this hypothesis, we randomly selected cervix cancer patients from 4 different categories thought to increasingly have poor prognosis. (n=16)

- Small primary and negative nodes
- Small primary with positive nodes
- Large primary with negative nodes
- Large primary with positive nodes

To our knowledge, most of previously published studies have attempted to relate the SUVmax of primary tumour with survival by utilizing various methods of obtaining a cutoff value that may fit their data. However, in addition to the limitation of small sample sizes and variable tumour types, no uniform predictive value for SUV has emerged. The independent and clinically useful prognostic potential of SUVmax still remains undecided.

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