



# Usefulness of the Primary Tumor SUVmax on Preoperative FDG-PET/CT as a Prognostic Indicator for Patients with Gynecologic Cancers

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## Abstract

<sup>18</sup>F-fluoro-2-deoxy-D-glucose positron emission tomography with computed tomography (FDG-PET/CT) is an important imaging modality for diagnosing many types of cancer. In gynecologic malignancies, the maximum standardized uptake value (SUVmax), one of the quantitative parameters measured on FDG-PET/CT, has been used not only for evaluating malignancy, but also for disease staging or treatment monitoring, although its prognostic impact remains controversial. This review focuses on the usefulness of SUVmax of the primary tumor on preoperative PET/CT as a prognostic indicator for patients with gynecologic cancers, and considers recent findings of our studies as well as those by others. In cervical cancer, a high SUVmax was correlated with positive lymph node metastasis and lymph-vascular space involvement in patients receiving radical hysterectomy. In endometrial cancer, a high SUVmax was also correlated with positive clinicopathological factors. Using optimal cut-off values of SUVmax, patients with a higher SUVmax showed significantly poorer overall survival and progression-free survival for both cancers. In ovarian cancer, SUVmax was useful for distinguishing malignant from borderline or benign tumors, while it had a limited prognostic role. In summary, the primary tumor's SUVmax is a non-invasive, easily-measurable biomarker for diagnosing malignancy as well as predicting clinical outcomes of patients with gynecologic cancers.

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## Introduction

Imaging is a significant part of the preoperative management of patients with gynecologic malignancies, in addition to pathological findings on biopsy or probe laparotomy. For the initial diagnosis, trans-vaginal ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) are usually performed. However, these conventional imaging tools might be insufficient to provide a correct preoperative evaluation of malignancy and tumor aggressiveness or estimate postoperative clinical outcomes.

<sup>18</sup>F-Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) has been clinically introduced over the past decade, and is now a well-established and useful imaging modality for diagnosing, staging, and treatment monitoring in patients with many types of cancer [1]. For a patient suspected of having malignant gynecologic tumors based on conventional imaging findings and/or elevated serum tumor markers, FDG-PET could be considered [2]. There have been several reports showing that FDG-PET combined with CT (FDG-PET/CT) is superior to other imaging modalities such as US, CT, and MRI for primary staging and the detection of recurrence in gynecologic cancer patients [2-4]. In fact, FDG-PET/CT has been used for distinguishing malignant from non-malignant or premalignant (borderline) diseases; however, it remains controversial for assessing the prognosis of patients with gynecologic tumors [4-6].

Recent studies revealed that the maximum standardized uptake value (SUVmax), a semi-quantitative and simplified measurement of the tissue deoxyglucose metabolic rate measured on PET/CT, is one of the most common and useful parameters not only for evaluating malignancy but also for assessing the prognosis of patients with several types of cancer [1]. In this review, we focused on the role of the primary tumor SUVmax on preoperative PET/CT as a prognostic indicator for patients with gynecologic malignancies including cervical, endometrial, and ovarian cancers who

underwent surgical treatment. We consider the data from both our recent studies and those of others, and discuss the usefulness of the primary tumor's SUVmax as a non-invasive biomarker of these gynecologic cancers.

### Cervical cancer

Cervical cancer is generally treated by surgery, radiotherapy, or both, with/without chemotherapy. Most patients with early-stage disease are treated with radical hysterectomy. Despite the generally good prognosis associated with stage I-II cervical cancer, significant numbers of patients develop recurrence following surgery [7]. Thus, in addition to the currently-used prognostic factors based on the pathological findings, more reliable and convenient prognostic markers are needed for the individualization of post-operative adjuvant therapy.

In cervical cancer, prior studies demonstrated the usefulness of PET/CT for staging or assessing lymph node metastasis [8,9]. However, the correlation between the primary tumor's FDG uptake and clinicopathological or prognostic impact remains controversial [10-13]. Our recent study [14] investigated SUVmax of primary tumors measured by preoperative FDG-PET/CT in 59 patients with stage IA2-IIB invasive cervical cancer undergoing radical hysterectomy. Our results demonstrated that SUVmax was significantly higher in patients with an advanced stage, positive lymph node metastasis, lymph-vascular space involvement, and large tumors. The overall survival (OS) and progression-free survival (PFS) of patients with a higher SUVmax were significantly lower compared with patients with a lower SUVmax, using an optimal cut-off value of 7.36 for OS and 5.59 for PFS [14]. When analyzed only in 39 patients with stage IB, OS and PFS in patients with a higher SUVmax were significantly lower using a cut-off value of 7.90 and 6.69 for OS and PFS, respectively [14]. In this study, the primary tumor's SUVmax was an independent prognostic factor for impaired PFS on multivariate analyses. These findings demonstrated that a high SUVmax was correlated with unfavorable clinical outcomes.

Consistent with our findings, Kidd et al. [10] showed that SUVmax was a prognostic indicator in stage IA2-IVB cervical cancer patients treated with surgery or chemo-radiotherapy. Xue et al. [11] also reported that SUVmax is predictive of disease-free survival in stage IB1-IVB cervical cancer patients treated with radiation therapy. In contrast, Cho et al. [12] demonstrated that a high pretreatment SUVmax was not predictive of recurrence in IB1-IVB cervical cancer patients treated with surgery or concurrent chemo-radiation. Crivellaro et al. [13] also showed that SUVmax was not associated with recurrence. The discrepancy among these studies might be due to treatment bias because their disease stages and treatment modalities were diverse. When focusing on surgically-treated early-stage (stage I-II) cervical cancer, Lee et al. [15] and Yun et al. [16] showed that a high SUVmax was correlated with impaired disease-free survival, which is consistent with our studies [14]. Taken together, these findings suggest that the primary tumor's SUVmax on preoperative PET/CT could be a useful prognostic indicator for surgically-treated patients with early-stage invasive cervical cancer.

### Endometrial cancer

Endometrial cancer is generally treated with hysterectomy with/without post-operative radiotherapy or chemotherapy. While endometrial cancer patients with stage I-II disease can achieve a favorable outcome with surgery alone, patients with advanced disease

or recurrence show poor survival. Several clinicopathological factors are used for the classification of relapse risks, and adjuvant therapy is applied for patients belonging to high-risk groups, although criteria for selecting patients remain controversial. Therefore, the identification of additional prognostic markers may be helpful for risk stratification and the individualization of adjuvant therapy.

Prior studies showed that a high FDG uptake within primary tumors evaluated by PET-CT was correlated with clinicopathological factors and aggressive biological characteristics of endometrial cancer [17,18]. Nakamura et al. [17] reported that the primary tumor's SUVmax was correlated with the histological grade. Antonsen et al. [18] showed that a high SUVmax was predictive of the presence of risk factors such as deep myometrial invasion and positive lymph node metastasis in endometrial cancer. In terms of the prognostic impact, Nakamura et al. [19] and Walentowicz-Sadlecka et al. [20] reported that SUVmax of the primary tumor was predictive of OS in endometrial cancer patients. Kitajima et al. [21] also showed that SUVmax was an independent factor for disease-free-survival. In contrast, recent meta-analysis by Ghooshkhanei et al. [22] demonstrated that the usefulness of SUVmax for classifying endometrial cancer patients into pre-defined risk groups may be limited and remains to be clarified.

Recently, we investigated the primary tumor SUVmax on preoperative FDG-PET/CT in 75 surgically-treated patients, including 63 with endometrial carcinoma and 12 with uterine carcinosarcoma [23]. Our results showed that SUVmax was higher in patients with stage II/III disease, a histology of grade 3 endometrioid adenocarcinoma and carcinosarcoma (but not of serous or clear cell adenocarcinoma), a positive results for lymph node metastasis, a positive result for lymph-vascular space involvement, and deep myometrial invasion. Furthermore, the OS and PFS of patients with a higher SUVmax were significantly lower compared with those of patients with a lower SUVmax using a cut-off value of 7.30 [23]. In addition, multivariate analyses demonstrated that the primary tumor's SUVmax was an independent prognostic factor for impaired PFS in 55 endometrioid adenocarcinoma patients. However, in this study, there was no significant difference in the OS or PFS between the high and low SUVmax groups in carcinosarcoma patients alone [23]. These findings suggest that the primary tumor's SUVmax may be a useful biomarker not only for stratification of the relapse risks, but also for predicting clinical outcomes of patients with endometrioid adenocarcinoma. Further studies are needed to clarify the prognostic impact of SUVmax in patients with specific histological types of endometrial neoplasm, such as serous adenocarcinoma, clear cell adenocarcinoma, and carcinosarcoma,

### Ovarian cancer

FDG-PET/CT is now widely used for primary staging, treatment monitoring, and the detection of recurrence in ovarian cancer patients. Furthermore, there have been several reports on the usefulness of FDG-PET/CT in the initial diagnosis of ovarian tumors; namely whether the tumor is malignant or benign/borderline [5,24]. Our recent study involving 160 patients suspected of having a malignant ovarian tumor demonstrated that the primary tumor SUVmax on preoperative FDG-PET/CT is useful for differentiating ovarian cancer from borderline or benign tumors with a high specificity and high positive predictive value using a cut-off level of 2.9 [24]. However, our data showed that it is difficult to distinguish borderline from benign tumors using SUVmax [24]. Similarly, Kitajima et al. [5] showed that

a cut-off SUVmax of 2.75 was optimal to separate benign/borderline and malignant ovarian tumors with high sensitivity and specificity.

In contrast to the usefulness of the primary tumor's SUVmax on FDG-PET/CT for the initial diagnosis of ovarian cancer, its prognostic impact remains controversial. Nakamura et al. [6] showed that a high SUVmax of the primary tumor was an important factor for identifying ovarian cancer patients with a poor prognosis. Chung et al. [25] also reported that the SUV distribution showed a significant correlation with the recurrence of ovarian cancer. In contrast, Risum et al. [26] showed that SUVmax of the primary tumor was not prognostic and FDG uptake could not be used to predict complete cytoreduction after primary surgery. This discrepancy might be due, at least in part, to variation of FDG accumulation depending on the histological subtypes of ovarian cancer: our study showed that SUVmax was lower with a clear cell or mucinous histology compared with serous or endometrioid types [24]. Further studies using sufficient numbers of patients with each histological subtype are needed to clarify the role of SUVmax on PET/CT as a prognostic indicator in ovarian cancer patients.

## Discussion and Future Perspectives

The FDG uptake in a tumor measured on PET/CT is influenced by multiple factors, such as the expression of glucose transporters (GLUT), cytoplasmic hexokinase activity, and variability of the cellular density or blood supply, the extent of hypoxia, cellular proliferation, and enzyme systems determining the metabolic activity [27]. In fact, Berger et al. [28] showed that low tumor cellularity and a high level of mucin were correlated with a lower FDG uptake in the mucinous type of carcinoma. The diversity of histological types and their variable biological characterization may further reduce the usefulness of SUVmax as a prognostic indicator in ovarian cancer patients as compared with cervical or endometrial cancers patients.

Another possible factor influencing the measured FDG uptake may be the size of active tumors. Kitajima et al. [5] showed that owing to the partial volume effect of a tiny lesion, the evaluation of early-stage ovarian carcinoma with a small solid component by PET/CT is limited. Prakash et al. [29] also reported that FDG-PET/CT is limited in its ability to identify lesions <1 cm, particularly those smaller than 5 mm. Thus, the lower SUVmax in patients with early-stage disease, showing a better prognosis, may partly be due to the smaller size of tumors.

As the primary tumors exhibit intratumoral FDG metabolic heterogeneity [30], SUVmax, although it is simple and easy to measure, may have limitations. Recently, several new metabolic parameters of FDG-PET/CT, in addition to SUVmax, were shown to be useful in patients with gynecologic cancers. Kitajima et al. [31] demonstrated that the metabolic tumor volume (MTV) and total lesion glycolysis (TLG) of the primary tumors were more useful for differentiating high-risk from low-risk endometrial cancer than SUVmax alone. Chung et al. [32] also reported that MTV was an independent prognostic factor for disease recurrence in endometrial cancer patients. Husby et al. [33] showed that MTV was useful for the identification of high-risk endometrial cancer patients. Consistent with this, MTV was shown to be an independent prognostic indicator of disease recurrence in patients with surgically-treated cervical cancer [34,35]. Chung et al. [36] also reported that pretreatment metabolic parameters such as MTV and TLG showed a significant association with recurrence in ovarian cancer patients, suggesting that these values can be useful quantitative criteria for disease

prognostication in patients with ovarian cancer. Further studies using multi-metabolic parameters of FDG-PET/CT, including SUVmax, MTV, and TLG, in combination with other non-invasive biomarkers, are needed to clarify the optimal prognostic indicator for gynecologic cancer patients.

## Conclusion

High SUVmax on preoperative PET/CT correlates with clinicopathological risk factors and less favorable clinical outcomes in cervical cancer and endometrial cancer patients. These findings suggest that the primary tumor's SUVmax may be a promising non-invasive prognostic indicator for risk stratification and the individualization of post-operative adjuvant therapy in patients with these diseases, although its usefulness as a prognostic indicator in ovarian cancer patients needs to be clarified by further studies.

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