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Letter to the Editor - Urologic Oncology

Title: “Future role of [18F]-FDG PET/CT in patients with bladder cancer in the new era of neoadjuvant immunotherapy ?”

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Dear editor,

We read with great interest the original article published by Marandino et al. entitled “[18F]Fluoro-Deoxy-Glucose positron emission tomography to evaluate lymph node involvement in patients with muscle-invasive bladder cancer receiving neoadjuvant pembrolizumab” [1]. This study reports for the first time the accuracy of [18F]-fluorodeoxyglucose ([18F]-FDG) positron emission tomography/computed tomography (PET/CT) in bladder cancer staging prior to neoadjuvant immunotherapy. Herein, we would like to raise several points of major interest. Immune checkpoint inhibitors (ICIs) have been progressively approved for a wide range of indications in advanced and metastatic malignancies in the past decade [2]. The activity and clinical benefit of ICIs are currently extensively investigated in the neoadjuvant settings in many tumor types, such as melanoma, non-small cell lung cancer (NSCLC), colon cancer, glioblastoma, sarcoma and, particularly in this article: bladder cancer [3–5]. Hence, there are critical needs to optimally select patients that will benefit the most from such a neoadjuvant therapy and to determine the best metrics to precisely measure treatment efficacy. Clinical utility of [18F]-FDG PET/CT in this indication had never been explored prospectively prior to the publication of the Marandino et al. manuscript [1]. While the role of [18F]-FDG PET/CT for prognostication and response assessment has been extensively demonstrated in patients with advanced NSCLC [6], advanced melanoma [7,8], and relapsed/refractory Hodgkin Lymphoma treated with ICIs [9,10], the literature remains scarce in patients with respect to bladder cancer. Thus, we read with great care the excellent scientific work of Marandino and colleagues that promotes awareness on the potential role of [18F]-FDG PET/CT in patients with muscle-invasive bladder cancer (MIBC) treated with neoadjuvant PD-1 blockade therapy.

This article confirms the diagnostic accuracy of [18F]-FDG PET/CT for lymph node staging in MIBC, which has previously been reported [11,12]. But most importantly, this study highlights the role of [18F]-FDG PET/CT in patient selection before neoadjuvant ICIs. In their comprehensive work, Marandino et al. emphasized the ability of [18F]-FDG PET/CT to select the optimal candidates for a neoadjuvant immunotherapy (chemotherapy-free) approach by excluding approximately 7% of patients with suspicious lymph node disease revealed by [18F]-FDG PET/CT while previously classified cN0 according to uroCT [1]. This is clinically significant since these cN+ patients may benefit from combined aPD(L)1 mAb plus aCTLA4 mAb immunotherapy [13,14] or from induction chemotherapy first, rather than from single neoadjuvant immunotherapy [15]. Of note, patients with enlarged pelvic lymph nodes (>8mm in the short axis on uroCT) were not included in this study, but [18F]-FDG PET/CT might have ruled out pelvic lymph node involvement in some of them, enabling these patients to benefit from neoadjuvant immunotherapy too [11,16]. Importantly, Marandino et al. reported that two patients classified cN0 at baseline progressed to cN+ after 3 cycles of neoadjuvant pembrolizumab, probably worsening their disease trajectory. Thus, predictive biomarkers are urgently warranted to tailor the use of immunotherapy in the neoadjuvant setting [17]. [18F]-FDG PET/CT has been reported to be of interest in this indication in other malignancies [8]. Interestingly, a higher [18F]-FDG uptake by tumor seems to be associated with elevated PD-1/PD-L1 expression in MIBC tumors, potentially guiding the decision to select patients for ICIs [18,19].

The spread of the use of neoadjuvant ICIs, highlights the issue of novel patterns of response and progression, such as pseudo-progression and hyperprogression. These patterns have to be kept in mind since they

could negatively impact patient management. First, pseudoprogression is an immune-related pattern of response defined as a transient increase followed by a decrease in tumor burden. Its incidence is highly variable between studies, ranging between 2% and 10%, depending on tumor type, delivered treatment, and the subset of patients [20]. The pseudoprogression incidence rate has been reported as ranging between 1.5% and 17% of patients with advanced urothelial carcinoma [21]. Thus, the majority of apparent early progressive disease visualized on [18F]-FDG PET/CT represents true progression rather than pseudoprogression. Its incidence seems to be limited in the neoadjuvant setting, but falsely considering these patients with progressive disease would lead to preclude surgery with curative intent. Another immune-related pattern of response to be taken into account is hyperprogression, defined as a rapid increase in tumor growth rate secondary to the use of anti-PD-1/PD-L1 agents, when compared to the expected growth rate in non-treated patients [22,23]. Such dramatic responses impair patient's outcome by making unresectable initially resectable tumors. Hyperprogression occurs with an incidence of 9% in solid tumors, and it is associated with a poor prognosis [22]. To date, such unfavorable response patterns to neoadjuvant ICIs have not been clearly identified in localized urothelial carcinomas [24].

Additionally, the increased use of ICIs in neoadjuvant settings highlights the relevant question of immune-related adverse events (irAEs). The frequency of irAEs in patients with MIBC treated with ICIs is underreported in the existing literature, and it has not been reported by Marandino et al either. IrAEs are well-known autoimmune side effects of ICIs that can involve almost every organ. IrAEs in patients with advanced MIBC treated with ICIs occur in up to 23% of patients, in the same range as patients with other solid malignancies [25]. [18F]-FDG PET/CT can reveal a wide range of irAEs [26–28], (e.g., sarcoidosis-like syndrome, thyroiditis, hypophysitis, enterocolitis, and pneumonitis) with an accuracy of 83% [29]. Regarding the most frequent irAEs, [18F]-FDG PET/CT has been proven to be an accurate tool for early detection of patients that will develop permanent hypothyroidism [30]. It has recently been reported that shared genetic factors may have an impact on the risk for irAEs and survival on ICIs in bladder cancer [31].

Finally, since the authors have demonstrated the interest of [18F]-FDG PET/CT in this indication, it seems important to discuss technical considerations. Marandino et al. did not specify whether “time-of-flight” acquisitions and/or point-spread-function correction algorithms were applied or not. These recently developed and now widespread technologies have enhanced detectability of subcentimeter foci of disease [32] and therefore may significantly impact performance of PET/CT for nodal staging [33]. Unfortunately, the use of PET protocol including forced diuresis to lower artifacts caused by concentrated urinary radioactivity has not been clearly stated in this article. Such a protocol has been shown to improve diagnostic performance with respect to nodal disease [34,35]. Regarding Marandino's study, the use of recent technologies and adapted protocols might have enhanced [18F]-FDG PET/CT performance for nodal staging both at baseline and during follow-up.

Overall, Marandino et al. reported for the first time the clinical value of [18F]-FDG PET/CT in the neoadjuvant ICIs in bladder cancer. To our knowledge such good performances might be improved further by the use of the most recent PET/CT technologies and optimized protocols. During follow-up, it has to be kept in mind that [18F]-FDG PET/CT can early detect most of irAEs, and picture atypical response patterns on immunotherapy such as pseudoprogression and hyperprogression. In that regard, we firmly believe that [18F]-FDG PET/CT will

have a place to tailor the use of neoadjuvant (immuno)therapy in MIBC patients together with other early stage tumor types.

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