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Scientific Article

Spatial Pattern of Intraprostatic Recurrence after Definitive External-Beam Radiation Therapy for Prostate Cancer: Implications for Focal Boost to Intraprostatic Dominant Lesion

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Purpose: We retrospectively investigated spatial pattern associations between primary and recurrent tumor sites after definitive external-beam radiation therapy (EBRT) for prostate cancer, using positron emission tomography/computed tomography (PET/CT) with a prostate-specific membrane antigen (PSMA)-targeted probe, ^{18}F-FSU-880.

Methods and Materials: We used data from our prior phase 2 trial involving patients who received PET/CT with ^{18}F-FSU-880, which was designed to evaluate the tumor detection efficacy of PSMA-PET/CT for recurrent prostate cancer. Data from patients with local intraprostatic recurrence detected by PSMA-PET/CT after definitive EBRT were retrospectively analyzed. The prostate and seminal vesicles were divided into 14 sections. Two diagnostic radiologists separately re-evaluated the intraprostatic location of the primary tumor on magnetic-resonance imaging and that of the recurrent tumor on PSMA-PET/CT, respectively, and the rate of overlap between primary and recurrent tumors was calculated. The overlap rate was defined as "the number of sections that overlapped between the primary tumor and recurrent tumor" divided by "the total number of sections of recurrent tumor". A recurrent tumor was considered to be at the same location as the primary tumor when the overlap rate was equal to or greater than 75%, and a partial overlap was defined as an overlap rate between 25 and 74%.

Results: Twelve patients had local recurrence detected by PSMA-PET/CT. The median time to diagnosis of local recurrence was 9.1 (range, 2.2-12.3) years after definitive EBRT. The recurrent tumor was detected at the same location in 25.0%, and a partial overlap was noted in 41.7%.

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Conclusions: Local intraprostatic recurrence after definitive EBRT often occurs at the same site or at a partially overlapping site adjacent to the primary intraprostatic dominant lesion. Our results support the merit of focal dose-escalation for intraprostatic dominant lesions in definitive EBRT.

Introduction

Definitive external-beam radiation therapy (EBRT) is one of the standard treatment modalities for nonmetastatic prostate cancer (PCa). Local intraprostatic recurrence is an important recurrence pattern that needs to be resolved.[1, 2] The effectiveness of focal dose escalation for an intraprostatic dominant lesion (IPDL) has been reported.[3, 4] The rationale of focal boosting is based on the hypothesis that local recurrence primarily originates from the primary tumor site. However, very few studies have investigated the association between the IPDL location before EBRT and recurrent tumor location.[5-10]

Radiolabeled prostate-specific membrane antigen (PSMA)-targeted positron emission tomography/computed tomography (PET/CT) has shown excellent diagnostic accuracy for the detection of lesions in the settings of both de novo and recurrent PCa.[11-13] Although its diagnostic effectiveness has been mainly examined in the detection of metastatic lesions, its marked potential to detect intraprostatic recurrence has been reported.[14] Therefore, we considered that PSMA-PET/CT may be useful in investigating the association between the IPDL location before EBRT and recurrent tumor location. However, to our knowledge, no study has investigated the spatial pattern association between primary and recurrent tumor sites employing PSMA-PET/CT.

We previously conducted a prospective phase 2 study that evaluated the tumor detection efficacy of PET/CT with a PSMA-targeted probe (^{18}F-FSU-880)[15] in patients with suspected recurrent prostate cancer after primary definitive therapy (jRCTs051180037).[16] In the current study, we conducted a retrospective analysis to investigate the spatial pattern association between primary and recurrent tumor sites after definitive EBRT for nonmetastatic PCa.

Methods and Materials

This study followed the tenets of the Helsinki Declaration, with approval from the institutional ethical review board (approval number: R3287).

Patients

We retrospectively reviewed clinical data of the patients registered in the phase 2 study[16] to search for eligible patients. The eligibility criteria were as follows: (1) received definitive EBRT as primary therapy; (2) local intraprostatic recurrence was detected on PSMA-PET/CT; and (3) magnetic-resonance imaging (MRI) examination of the prostate was performed at the initial diagnosis. Patients with distant metastasis at the initial diagnosis were excluded.

Determination of intraprostatic tumor at initial diagnosis and recurrence

The primary IPDL and its location were re-evaluated using MR images before primary therapy (pre-RT MRI) based on the consensus of 2 board-certified diagnostic radiologists who specialized in diagnosis of pelvic MRI (YM and AK) and who were blinded to information regarding the location of any recurrent tumor. Diagnosis of primary IPDL was generally based on Prostate Imaging Reporting and Data System (PI-RADS) version 2.1 criteria.[17] The recurrent tumor and its location were re-evaluated using PSMA-PET/CT (post-RT PSMA-PET/CT) based on the consensus of 2 board-certified nuclear medicine physicians (YN and TO), who were also blinded to information regarding the location of primary IPDL. Details of image analysis and diagnostic methods were previously reported.[16]

Statistical analysis

The prostate was divided into 12 sections (left/right, anterior/posterior, and base/midgland/apex), and the

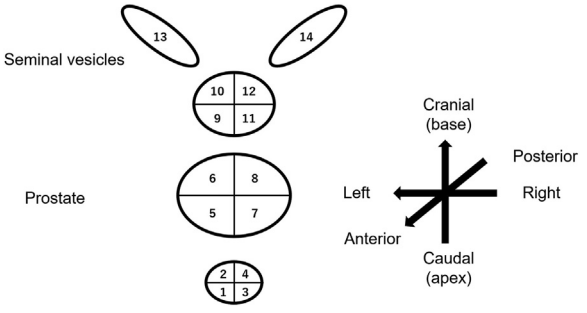

Figure 1 Diagram used for diagnosis of intraprostatic tumor location. The prostate was divided into 12 sections (left/right, anterior/posterior, and base/midgland/apex; section numbers 1-12), and the seminal vesicles were divided into 2 sections (left/right; section numbers 13 and 14).

Table 1 Patient and treatment characteristics

Age at the EBRT (years)	
Median (range)	61 (52-68)
Age at diagnosis of local recurrence (years)	
Median (range)	70 (62-79)
Clinical T stage at initial diagnosis, n (%)	
T1c	1 (8.3)
T2a	3 (25.0)
T2b	2 (16.7)
T2c	0 (0.0)
T3a	3 (25.0)
T3b	3 (25.0)
T4	0 (0.0)
PSA at the initial diagnosis (ng/mL)	
Median (range)	19.1 (4.4-70.1)
PSA at the diagnosis of local recurrence (ng/mL)	
Median (range)	2.38 (1.6-14.4)
Gleason score at the initial diagnosis, n (%)	
3+3	0 (0.0)
3+4	3 (25.0)
4+3	2 (16.7)
4+4	5 (41.7)
4+5	1 (8.3)
5+4	1 (8.3)
5+5	0 (0.0)
NCCN risk classification at the initial diagnosis, n (%)	
Favorable intermediate risk	1 (8.3)
Unfavorable intermediate risk	1 (8.3)
High risk	3 (25.0)
Very high risk	7 (58.3)
EBRT method and dose, n (%)	
IMRT	
78 Gy in 39 fractions	7 (58.3)
74 Gy in 37 fractions	3 (25.0)
54 Gy in 15 fractions	1 (8.3)
Carbon-ion radiation therapy	
57.6 Gy relative biologic effectiveness in 16 fractions	1 (8.3)
Time to local recurrence after EBRT (years)	
Median (range)	9.1 (2.2-12.3)
Hormonal sensitivity at the diagnosis of local recurrence	
Castration sensitive	11 (91.7)
Castration resistant	1 (8.3)

Abbreviations: EBRT = external-beam radiation therapy; IMRT = intensity modulated radiation therapy; NCCN = the National Comprehensive Cancer Network (risk classification ver. 2. 2023); PSA = prostate-specific antigen.

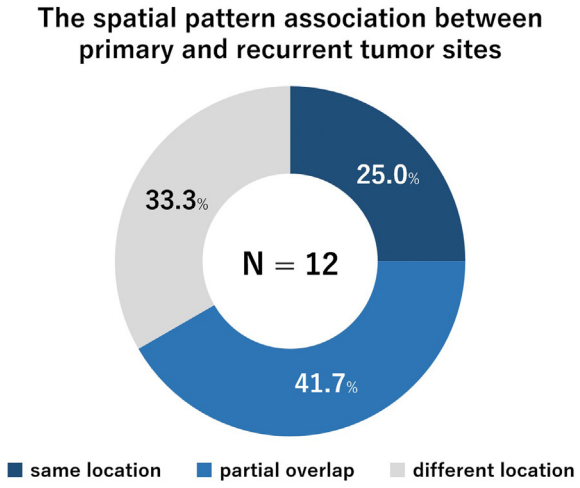

Figure 2 Results of spatial pattern association between primary and recurrent tumor sites.

seminal vesicles were divided into 2 sections (left/right) (Fig. 1). The primary IPDL and recurrent tumor were judged separately as present or absent in each section, as described above. The principal investigator (RA) reviewed the results of rereviewed diagnostic images at both initial diagnosis and recurrence and calculated the rate of overlap of the primary IPDL and recurrent tumor. The overlap rate (OR) was defined as "the number of sections that overlapped between the primary IPDL and recurrent tumor" divided by "the total number of sections of recurrent tumor". A recurrent tumor was considered to be at the "same location" as the primary tumor when OR was equal to or greater than 75%; a "partial overlap" was identified when OR was between 25 and 74%; and a "different location" was deemed when OR was less than 25%.

Results

Among the 72 patients who received PET/CT with ^{18}F-FSU-880 in our phase 2 trial, intraprostatic recurrence was recorded in 13 patients, and they met the eligibility criteria. Among them, the site of recurrence was diagnosed as located outside of the prostate at re-evaluation in one patient. Therefore, this patient was excluded, and the remaining 12 patients were included in the current analysis.

The median patient age was 70 (range, 62-79) years old at diagnosis of local recurrence and 61 (range, 52-68) years old at initiation of definitive RT. The median PSA level was 2.38 (range, 1.6-14.4) ng/mL at diagnosis of local recurrence and 19.1 (range, 4.4-70.1) ng/mL at initial diagnosis. Approximately 60% of the patients (n = 7) showed a GS sum ≥8, and half of the patients (n = 6) had ≥T3a disease. As primary definitive RT, the majority of patients (83.4%, n = 10) received conventional fractionated intensity modulated radiation therapy (IMRT) with a median prescribed dose of 78 Gy (range, 74-78) to the prostate at 2 Gy per fraction. The other treatments consisted of hypofractionated IMRT (54 Gy in 15 fractions) in 8.3% (n = 1) and carbon-ion radiation therapy (57.6 Gy relative biologic effectiveness in 16 fractions) in 8.3% (n = 1). Hormonal therapy was administered in all cases. The median time to diagnosis of local recurrence was 9.1 (range, 2.2-12.3) years after definitive EBRT. Local recurrence was the initial pattern of clinical recurrence in 83.3% (n = 10), and local recurrence and pelvic/para-aortic lymph node metastasis was simultaneously diagnosed in 8.3% (n = 1). In the remaining 8.3% (n = 1), initial patten of clinical recurrence was pelvic lymph node, which was definitively treated with pelvic irradiation,[18] and local recurrence was detected during follow-up. Among the 12 patients, 91.7% (n = 11) had castration-sensitive disease, and 8.3% (n = 1) had castration-resistant disease at diagnosis of local recurrence. Details of patient and treatment characteristics are summarized in Table 1.

The recurrent tumor was detected at the "same location" in 25.0% (n = 3) of cases, in an area showing "partial overlap" in 41.7% (n = 5), and at a "different location" in the remaining 33.3% (n = 4) (Fig. 2). Details of primary IPDL and recurrent tumor locations are shown in Fig. 3.

Discussion

To the best of our knowledge, this is the first study to investigate the spatial pattern of association between primary tumor sites and intraprostatic recurrence sites after definitive radiation therapy for nonmetastatic PCa using PSMA-PET/CT. All patients included in the current analysis received modern definitive EBRT. Two-thirds of the recurrent tumors were either at the same site or a partially overlapping site adjacent to the primary IPDL.

Several previous studies investigated the spatial pattern association between primary and recurrent tumor sites after definitive EBRT for nonmetastatic PCa.[5-10] The majority of these studies reported that post-EBRT local recurrence occured at the site of the primary IPDL.[5-9] According to an investigation using MR imaging and MR spectroscopic imaging by Arrayeh et al, the dominant recurrent tumor was observed at the same location as the primary IPDL in 8 of 9 patients treated with definitive EBRT (89%).[5] Similarly, according to an investigation of 12 patients who developed intraprostatic recurrence after EBRT, local recurrence was shown to originate within the initial tumor site in all cases (100%).[6] Our observations were consistent with these findings from previous studies. In the current study, recurrent tumors were at the same location in 25% of the cases (n = 3/12) and shared an overlapping area (partial overlap) in 41.7% (n = 5/12). In the latter cases, although speculative, it is reasonable to consider that residual tumors after EBRT expanded to areas adjacent to the original recurrent site. Therefore, in total, two-thirds of the recurrent tumors were considered to originate from the pretreatment IPDL. The

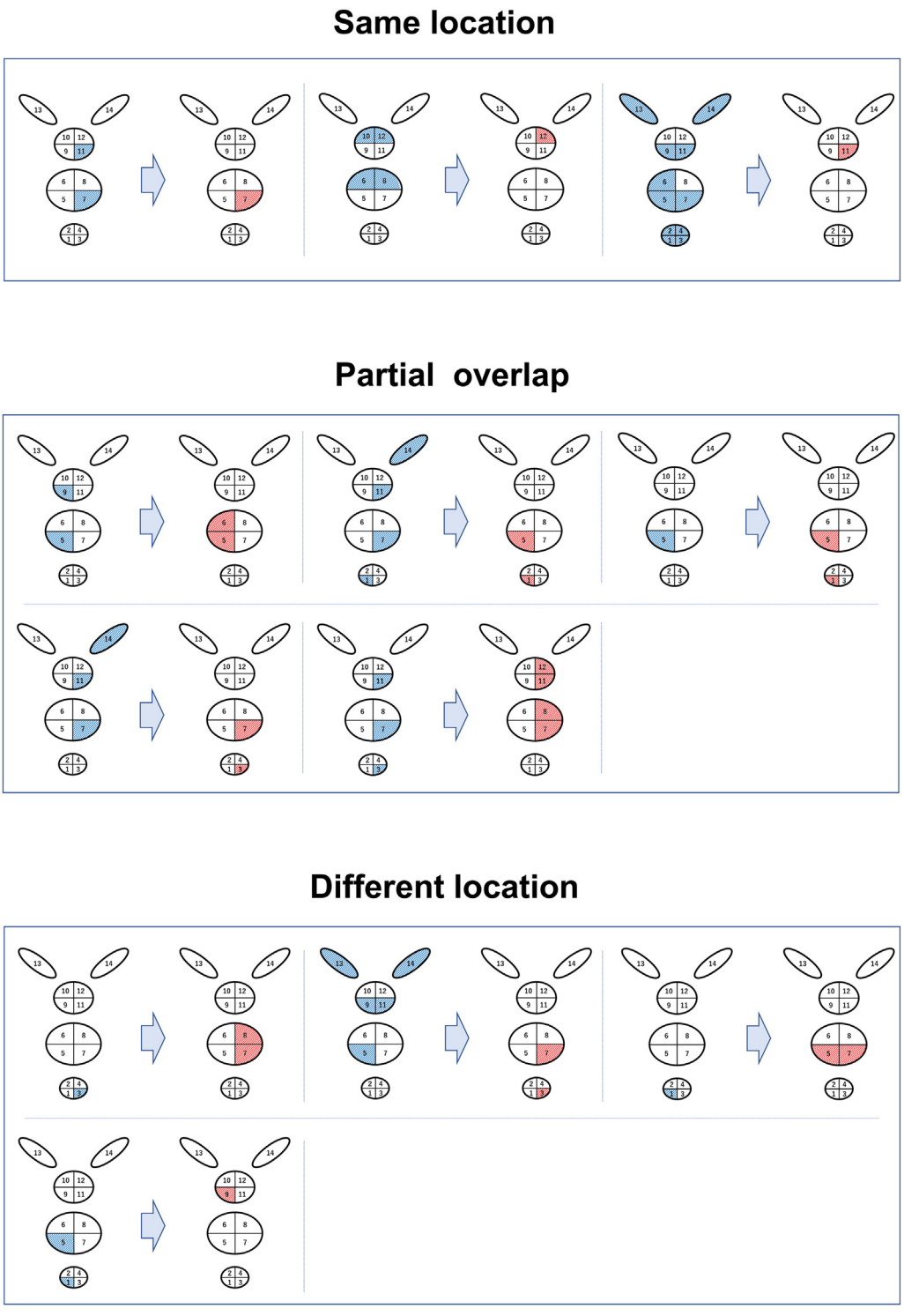

Figure 3 The details of sites of disease location. Sections with blue hatching indicate location of primary tumors. Sections with red hatching indicate location of recurrent tumors.

effectiveness of focal boost to IPDL has been proposed to improve disease control without increased toxicity. According to the FLAME phase III trial, which evaluated the benefit of adding focal boost to IPDL,[4] the biochemical disease-free survival rate was significantly better in the focal-boost arm (HR, 0.45; 95% CI, 0.28-0.71; $P < .001$). Our results provide information supporting the rationale of adding focal boost to IPDL.

Despite growing enthusiasm and data supporting the benefits of focal dose-escalation to IPDL, the appropriate candidates for this EBRT method have not been established. Currently available modern IMRT in combination with

highly sophisticated image guided radiation therapy (IGRT) techniques have achieved excellent tumor control.[19-21] The recurrence rate among intermediate-risk PCa was low even without focal dose-escalation. According to the phase 2 study of moderate hypofractionated IMRT (70 Gy in 28 fractions), the biochemical failure-free survival rate was 97.4% at 5 years.[20] Similarly, according to a retrospective analysis, which investigated the impact of prostate position-based IGRT among intermediate-risk PCa treated with IMRT (76 Gy in 38 fractions), the biochemical failure-free rate was 94.9% at 10 years.[21] On the other hand, for the high-risk PCa population, there is still room for improvement regarding tumor control by local dose-escalation. In the aforementioned FLAME phase 3 trial, which demonstrated the improvement of biochemical disease-free survival by adding focal dose-escalation, the study population consisted mostly of high-risk PCa (84%).[4] In the current study, more than 80% of the patients (n = 10/12) had high-risk or very high-risk PCa at the initial diagnosis. Therefore, although somewhat speculative, focal dose-escalation may be most beneficial among high-risk and very high-risk PCa. Further investigations are warranted to identify the optimal candidates for focal dose-escalation to IPDL.

Our study had several limitations, including the small number of subjects. Only selected cases among those patients who developed biochemical failure after primary EBRT underwent PSMA-PET/CT. Because of selection bias, cases included in this study may not accurately reflect the overall population developing local recurrence. In addition, different imaging modalities were used for the diagnosis of tumor locations: PSMA/PET-CT versus MRI. The lower spatial resolution of PET-CT compared with MRI and slight positional deviations during the fusion process of CT and PET images may decrease the accuracy of the data regarding recurrent tumor positions. Furthermore, as local recurrence was diagnosed solely based on findings of radiographic images, our results lack pathologic confirmation. Therefore, the results regarding the spatial pattern association between primary and intraprostatic recurrence sites after definitive EBRT are not conclusive but hypothesis-generating. Despite these limitations, our results could serve as baseline data due to the lack of high-level evidence regarding this issue. Given the growing trend toward the application of focal boost in definitive EBRT, our findings are of particular importance.

In conclusion, local recurrence after definitive EBRT often occurs at the same site or at a partially overlapping site adjacent to the primary IPDL. Therefore, our results support the merit of focal dose-escalation to IPDL in definitive EBRT for nonmetastatic PCa.

Disclosures

Rihito Aizawa, Tomoaki Otani, Aki Kido, Takayuki Goto, Kimihiko Masui, Takayuki Sumiyoshi, Yuki Kita, Yuji Nakamoto, Takashi Kobayashi, and Takashi Mizowaki report receiving funds for a corporate clinical trial from Novartis Pharma K.K. Takashi Kobayashi reports receiving funds and honoraria for lectures from Janssen, Astellas, Bayer, Astra Zeneca, and Chugai.

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