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The relationship of *TMPRSS2-ERG* gene fusion between primary and metastatic prostate cancers

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Abstract

Recent studies have revealed the presence of *TMPRSS2-ERG* gene fusion in both primary and metastatic prostatic cancers (PCAs). However, the relationship between primary and corresponding metastatic PCAs with respect to the status of this gene fusion remains unclear. Using fluorescence *in situ* hybridization, we evaluated the rearrangement of the ERG gene in the radical prostatectomy (RP) specimens and corresponding lymph node metastases from 19 patients with PCA. The mean age of the patients was 61 years and the median Gleason score in the RP specimens was 7 (4+3). PCA was unifocal in 6 cases and multifocal in 13 cases, including 10 with 2 foci and 3 with 3 foci. In the primary PCAs, rearrangement of the ERG gene was observed in 13 cases and associated with deletion of the 5' ERG gene in 8 cases. In the metastases, the ERG rearrangement was present in 10 cases and associated with deletion of the 5' ERG gene in 6 cases. In unifocal PCAs, the status of the ERG rearrangement was concordant between the primary PCA and metastasis in 5 of 6 cases. In multifocal PCA, despite a significant interfocal discordance, the status of the ERG rearrangement was concordant between the index (largest) primary tumor focus and metastasis in all 13 cases. Our study demonstrates a close relationship of the TMPRSS2-ERG gene fusion status between primary and metastatic PCA. The concordance of the ERG gene rearrangement status between the index primary tumor focus and metastasis suggests that metastasis most likely arises from the index tumor focus in multifocal PCA.

Keywords

TMPRSS2-ERG gene fusion; prostate cancer; metastasis; multifocality

Introduction

Recent studies have demonstrated a unique recurrent gene fusion in most prostate cancers (PCAs).[1-3] This gene fusion is characterized by fusion of the 5' region of the *TMPRSS2* gene with the 3' region of the *ERG* gene. *TMPRSS2* is regulated by androgen in the prostate,[4] and *ERG*, a member of the *ETS* family, is an oncogene.[5] The *TMPRSS2-ERG* gene fusion leads to aberrant function of *ERG* in the prostate, which is believed to be involved in

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the oncogenesis of PCA.[1] Other members of the *ETS* family, such as *ETV1*, *ETV4* and *ETV5*, also fuse with the 5' end of *TMPRSS2*, although at a much lower frequency.[6,7] Likewise, other genes, such as *SLC45A3 and NDRG1*, may fuse with the 3' region of *ETS*.[8,9] Nonetheless, the *TMPRSS2-ERG* gene fusion accounts for the majority of recurrent gene fusions in PCA.[10]

The *TMPRSS2-ERG* gene fusion is also highly prevalent in metastatic PCA.[11,12] Mehra *et al* found that all the *TMPRSS2-ERG* gene fusion in metastatic PCA was associated with deletion of the 5' end of *ERG* gene.[11] Furthermore, multiple metastases from an individual patient shared the same pattern of *TMPRSS2-ERG* gene fusion, suggesting that metastases developed as a result of clonal expansion of a single focus of primary PCA. However, the relationship of TMPRSS2-ERG gene fusion between primary and metastatic PCA remains unclear. In the current study, we compared the gene fusion status (presence or absence) between primary PCA in radical prostatectomy specimens and their corresponding metastases in lymph nodes.

Materials and methods

Case Selection and Pathologic Evaluation

With the approval of Institutional Review Board (IRB), we retrospectively searched our pathology file at The University of Texas MD Anderson Cancer Center and selected 19 patients who underwent radical prostatectomy (RP) and pelvic lymph nodes dissection from 2003 to 2009. All patients had primary PCA in the RP specimens and metastatic PCA in the pelvic lymph nodes. No patient had received treatment for PCA before RP. Pathologic features were collected from histologic examination of the specimens. In the RP specimens, each tumor focus was graded according to the Gleason grading system, and the tumor volume was calculated using a previously described formula.[13] Patients' demographic and clinical features were obtained from medical records.

Determination of the *TMPRSS-ERG* Gene Fusion

To evaluate the *TMPRSS2-ERG* gene fusion in the primary and metastatic PCA, we analyzed the rearrangement of the ERG gene with break-apart fluorescence *in situ* hybridization (FISH). The break-apart probes, a rhodamine-labeled 5′ *ERG* probe (*BAC RP11-95I21*) and a fluorescein isothiocyanate-labeled 3′ *ERG* probe (*BAC RP11-476D17*), were obtained from Children's Hospital of Oakland Research Institute (Oakland, CA). Tissue pretreatment was performed using Paraffin Pretreatment Kit I (Vysis, Des Plaines, IL), and hybridization and washing were performed using Vysis hybridization reagents, following the manufacturer's protocols. The specificity and quality of the probes were confirmed by hybridization to the metaphase spread of normal peripheral lymphocytes. A mean of 100 cells was evaluated per tumor focus.

Results

The average age of patients was 61 years (range 43-76 years). In the RP specimens, the PCA was unifocal in 6 cases and multifocal in 13 cases (Table 1). In the RP specimens, 23 tumor foci were in the peripheral zone and 8 foci were in the transition zone. Two tumor foci involved multiple zones and its zonal origin was considered undetermined. The RPs with unifocal PCA had a median Gleason score 9 (4+5) (range 7-9) and a mean tumor volume was 7.45 cm^3 (range 2.80-12.16 cm^3). The multifocal PCA included 2 foci in 10 cases and 3 foci in 3 cases (Figure 1A). In the RPs with multifocal PCA, the index (largest) tumor focus had a mean volume of 3.80 cm^3 (range 1.44 10.08 cm^3) with a median Gleason score of 7 (4+3; range 7-9), and the secondary tumor foci had a mean volume of 0.27 cm^3 (range

0.01-2.16 cm^3) with a median Gleason score of 6 (3+3) (range 6-7). While the secondary tumor foci (n=16) were located in either the transition zone (n=8; Figure 1B) or peripheral zone (n=8; Figure 1C), all the index tumor foci were located in the peripheral zone (Figure 1D). All patients received dissection of the pelvic lymph nodes, and a mean number of 14 (range 4-41) lymph nodes were removed. Metastatic PCA was present in all cases and a mean number of positive lymph nodes was 2 (range 1-6) (Figure 2).

The rearrangement of the *ERG* gene was evaluated in all tumor foci of each RP specimen using the break-apart probes (Table 1). In FISH analysis, the normal pattern of the *ERG* gene showed 2 pairs of colocalized green and red signals in the nuclei (Figure 1B and 1C), rearrangement of the *ERG* gene was characterized by only 1 pair of colocalized green and red signals in the nuclei (Figure 1 D). The other pair in the ERG rearrangement was broken apart, resulting in deletion or translocation of the red signal (the 5' *ERG* gene). In 5 of the 6 patients with unifocal PCA, *ERG* rearrangement was observed. In 8 of the 13 patients with multifocal PCA, *ERG* rearrangement was present either in the index tumor focus only (n=4), a secondary tumor focus only (n=2) or both (n=2).

The rearrangement of the *ERG* gene was also evaluated in metastatic PCA in the lymph nodes. The *ERG* rearrangement was observed in 10 cases, and the rearrangement was associated with deletion of the 5' *ERG* gene in 6 cases (Figure 2).

The status of the *ERG* gene rearrangement was compared between the primary tumor foci and metastasis in each patient. Among the 6 cases of unifocal PCA, there was a concordance of the *ERG* gene rearrangement status between the primary PCA and metastasis in 5 cases, including rearrangement in 4 cases and no rearrangement in 1 case. Among the 13 cases of multifocal PCA, although 6 cases showed an interfocal heterogeneity of the *ERG* gene rearrangement status, all cases showed a concordance of the *ERG* gene rearrangement status between the primary index tumor focus and the metastasis.

Discussion

Our study demonstrates a close relationship between primary and metastatic PCA with respect to the status of TMPRSS2-ERG gene fusion. Like primary PCA in our study, the majority of metastatic prostate cancers carried the TMPRSS2-ERG gene fusion, which was associated with either deletion or translocation of the 5' ERG gene. Furthermore, we compared the gene fusion status between the metastasis and its corresponding primary PCA in the RP specimen. In patients with unifocal disease in the RP specimen, the *TMPRSS2-ERG* gene fusion status was concordant between the primary tumor and metastasis in most cases. In patients with multifocal disease in the RP specimen, although there was significant interfocal heterogeneity of TMPRSS2-ERG gene fusion status in the primary PCA, the TMPRSS2-ERG gene fusion status was concordant between the index tumor focus and the metastatic disease, suggesting that the metastatic disease likely originated from the index tumor focus.

Since the discovery of TMPRSS2-ERG gene fusion in PCA, there has been considerable interest in the clinical significance of this gene fusion. Although some studies have reported that the presence of TMPRSS2-ERG gene fusion in PCA is associated with an unfavorable prognosis,[15,16] findings from other studies have not confirmed this association.[17,18] Recently, Attard *et al*[17] reported that duplication of TMPRSS2-ERG gene fusion is associated with a significantly worse prognosis, a finding that has been supported by a subsequent study [18]; however, this duplication is not specific to the TMPRSS2-ERG locus and likely reflects a general increase in chromosome copy number due to genetic instability

in aggressive PCA.[18] Therefore, TMPRSS2-ERG gene fusion is likely an early event in PCA oncogenesis but may not be a major factor in determining the patient's outcome.[19,20]

The majority of primary PCAs are multifocal.[13] Separate tumor foci are likely to arise independently in the same prostate gland, as evidenced by discordant patterns of allelic loss among various tumor foci.[21] Several groups have attempted to study TMPRSS2-ERG gene fusion in multifocal PCAs.[22,23] Although the TMPRSS2-ERG gene fusion status usually demonstrates an intrafocal homogeneity, this status in multifocal PCA demonstrates a significant interfocal heterogeneity. Previous studies found that about 40-50% of RP specimens with multifocal PCA showed discordant *TMPRSS2-ERG* gene fusion status.[22,23] In our study, 6 of 13 (46%) multifocal PCAs also showed an interfocal heterogeneity of the *TMPRSS2-ERG* gene fusion status, supporting that different tumor foci in the same prostate gland may arise independently from clonal expansion.

In a previous study, we found that *TMPRSS2-ERG* gene fusion is associated with the zonal origin of PCAs.[24] While this gene fusion is prevalent in PCAs arising from the peripheral zone, it is uncommon in PCAs arising from the transition zone. In the current study, only 1 of 8 (12.5%) PCAs of the transition zone showed ERG rearrangement. In contrast, 12 of 25 (48%) PCAs of the peripheral zone showed ERG rearrangement. Therefore, the findings of the current study support our previous observation that the TMPRSS2-ERG gene fusion in the transition zone is significantly less common than in the peripheral zone, although it may not be completely absent.

Several studies have demonstrated the presence of TMPRSS2-ERG gene fusion in the majority of metastatic PCA.[11,12,25] Using 30 metastatic tissue samples acquired by rapid autopsy tissue procurement, Mehra *et al* found several variants of TMPRSS2-EST gene fusion. The EST gene most commonly involved in gene fusion was ERG, followed by ETV1 and ETV4. Interestingly, they also found that TMPRSS2-ERG gene fusion in all metastases was associated with the deletion of the 5' ERG gene. However, in the current study, although the majority of ERG rearrangement was associated with the deletion, the gene rearrangement in 5 cases was associated, instead, with translocation. Similarly, a study using circulating PCA cells from patients with castration-resistant metastatic PCA found that TMPRSS2-ERG gene fusion was associated with translocation of the 5' ERG gene in 34% of the cases.[25] Therefore, TMPRSS2-ERG gene fusion in metastatic PCA is not exclusively associated with the deletion of the 5' ERG gene.

PCA metastases are often present in various anatomic locations, such as lymph nodes, bone, liver and lung. Several studies have attempted to investigate whether multifocal metastases arise from a single focus of primary PCA. [11,12,26] Using high-resolution genomewide analysis of single nucleotide polymorphisms and copy-number alterations, Liu *et al* found that most metastatic PCAs have monoclonal origins and maintain a unique signature copy-number pattern of the primary PCA.[26] FISH analyses also demonstrated that various foci of metastatic PCA within an individual specimen harbored the same TMPRSS2-ERG gene fusion pattern. Despite a significant interfocal heterogeneity in multifocal primary PCA, multifocal metastatic PCA most likely arises from a single focus of primary PCA.[11,12] These observations also imply that TMPRSS-ERG gene fusion is likely an early event and is not required for metastasis.

Perner *et al*[12] also studied the relationship between the primary PCA and metastatic disease with respect to TMPRSS2-ERG gene fusion status. They found that there was generally concordance of the ERG gene rearrangement status between the index tumor focus in multifocal PCA and the metastasis, despite discordance in a small subset of cases; furthermore, when multifocal PCA contained a tumor focus with ERG rearrangement and

another without the rearrangement, the metastatic disease showed the ERG gene rearrangement in all cases, suggesting that metastatic disease likely arose from the tumor focus with the ERG rearrangement. In the current study, we found concordance of the ERG rearrangement status between the index tumor focus and the metastasis in all cases of multifocal PCA, suggesting that the metastasis most likely arose from the index tumor focus. But it cannot be excluded that the metastasis may also arise from the secondary focus, particularly in the patients whose index and secondary tumor foci show similar pattern of the TMPRSS2-ERG gene fusion. Although metastatic PCA is not routinely given a Gleason score, we found that the metastatic PCA in the current study had a Gleason score of at least 8 (4+4). The high Gleason score in the metastatic PCA favors that it likely arises from the index tumor focus, as the index tumor focus had a higher Gleason score than the secondary tumor focus in all multifocal PCAs except for one case in our study. Six patients with multifocal PCA in our study contained one tumor focus with the ERG rearrangement and another without rearrangement. Four of the 6 patients showed rearrangement of the ERG gene in the metastases, and the other 2 patients did not have rearrangement in the metastases, despite that they had the ERG rearrangement in the primary tumor (both in the secondary focus), including one with deletion and the other with translocation. Thus the metastasis may also arise from the tumor focus without rearrangement of the ERG gene in multifocal PCA.

The current study has some limitations. Although the definition of index tumor focus in multifocal PCa was originally based on the tumor size, other criteria, such as Gleason score and tumor stage, may also be used to determine the index tumor focus in multifocal PCa.[27] In the current study, we used the original definition (tumor size) to determine the index tumor. Thus our findings remain to be verified in the index tumors based on different criteria. In 7 cases of multifocal PCA, the ERG rearrangement status in the secondary tumor focus was similar to that in the index tumor focus, which raises the possibility that the metastasis may have arisen from the secondary tumor focus in these cases. In 1 case, the primary PCA had the gene fusion while the metastasis lacked it, probably because the large tumor focus resulted from the fusion of several separate tumor foci. Finally, the number of cases in our study was limited by the availability of specimens. Further study in a large cohort of patients may help to further elucidate the relationship of TMRPSS2-ERG gene fusion between primary and metastatic PCA.

Acknowledgments

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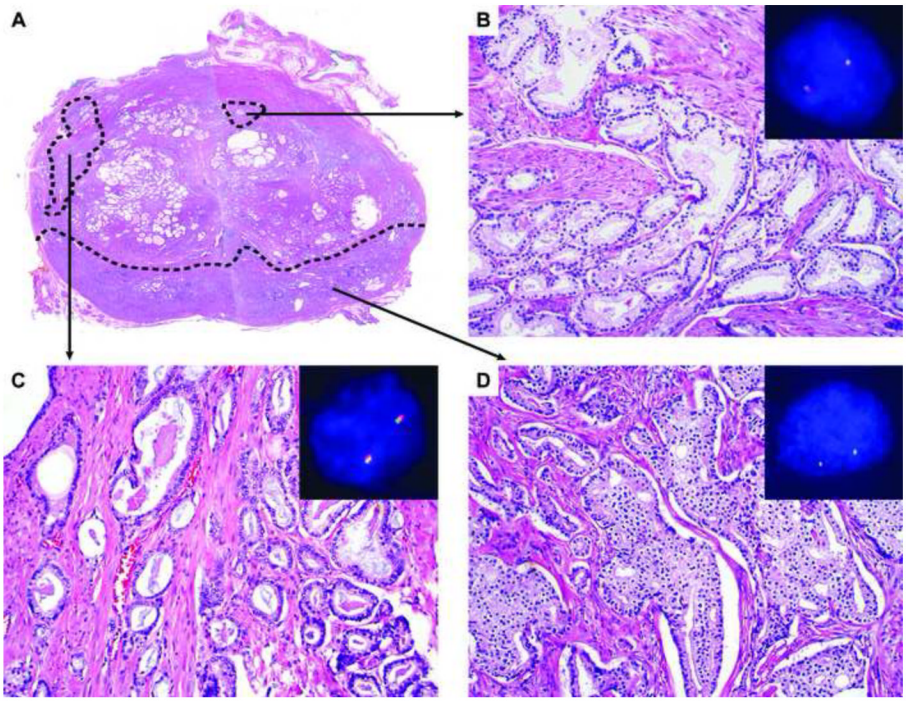

Figure 1.
The TMPRSS2-ERG gene fusion in primary prostate cancer. Three separate tumor foci, two in the peripheral zone and one in the transition zone, are present in a cross-section of the prostate (A). The tumor focus in the transition zone had normal ERG arrangement (B). The smaller tumor focus in the peripheral zone has normal ERG arrangement (C). The larger (index) tumor focus in the peripheral zone shows ERG rearrangement with deletion of the 5' ERG gene (D).

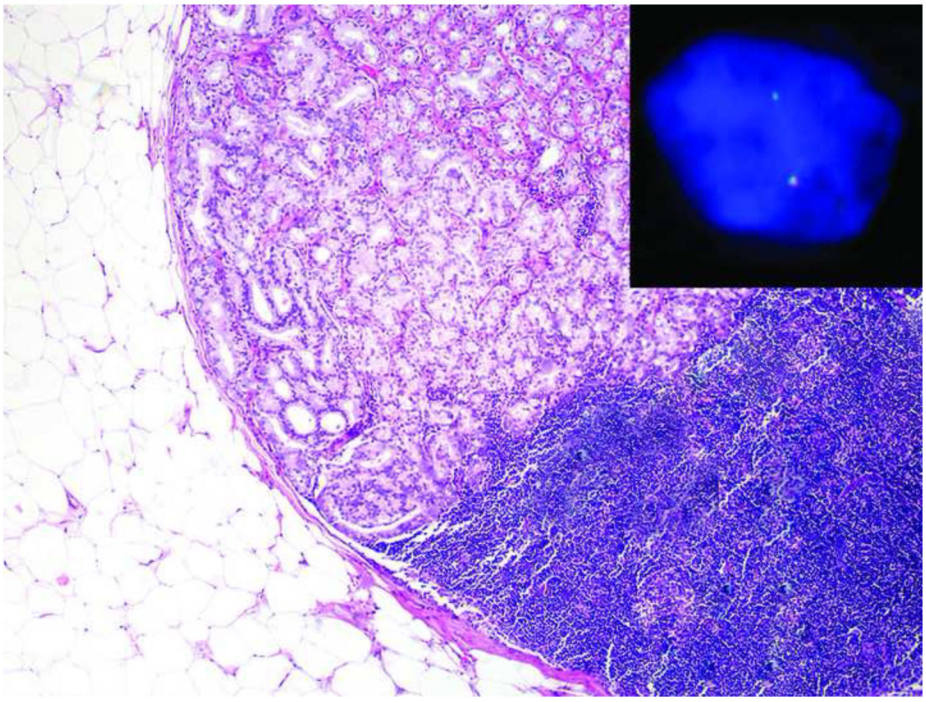

Figure 2.
The TMPRSS2-ERG gene fusion in metastatic prostate cancer. Metastatic prostate cancer in a lymph node shows ERG rearrangement with deletion of the 5’ ERG gene.

Table 1

Summary of pathologic features and *TMPRSS2-ERG* gene fusion status in primary and metastatic prostate cancer

Case No.	Metastasis gene fusion status	Primary tumor											
		Index tumor				Secondary tumor #1				Secondary tumor #2			
		GS	Vol. (cm^3)	Fusion status	Zone	GS	Vol. (cm^3)	Fusion status	Zone	GS	Vol. (cm^3)	Fusion status	Zone
1	Trans.	5+4	3.36	Trans.	PZ								
2	Neg.	4+3	5.60	Del.	PZ								
3	Trans.	4+5	12.16	Trans.	UZ								
4	Del.	4+5	2.80	Del.	PZ								
5	Trans.	4+5	9.60	Trans.	UZ								
6	Neg.	4+3	11.20	Neg.	PZ								
7	Neg.	4+3	2.00	Neg.	PZ	3+3	0.17	Trans.	PZ				
8	Neg.	4+3	2.87	Neg.	PZ	3+3	0.08	Neg.	PZ				
9	Del.	4+5	4.20	Del.	PZ	3+3	0.01	Neg.	PZ				
10	Trans.	3+4	1.44	Trans.	PZ	3+4	0.35	Neg.	PZ				
11	Del.	4+3	1.92	Del.	PZ	3+4	0.50	Del.	TZ				
12	Del.	4+5	10.08	Del.	PZ	3+3	0.01	Neg.	TZ				
13	Neg.	4+3	1.92	Neg.	PZ	3+3	0.05	Neg.	TZ				
14	Del.	4+5	4.00	Del.	PZ	3+3	0.03	Del.	PZ				
15	Neg.	4+4	6.57	Neg.	PZ	3+4	2.16	Neg.	TZ				
16	Neg.	4+5	2.52	Neg.	PZ	4+3	0.11	Neg.	PZ				
17	Del.	4+5	2.04	Del.	PZ	3+3	0.13	Neg.	PZ	3+3	0.01	Neg.	TZ
18	Neg.	4+3	3.20	Neg.	PZ	3+3	0.12	Neg.	TZ	3+3	0.10	Neg.	TZ
19	Neg.	4+5	7.20	Neg.	PZ	3+3	0.44	Del.	PZ	3+3	0.03	Neg.	TZ

Del., ERG gene rearrangement associated with deletion; GS, Gleason score; Neg., negative for *ERG* gene rearrangement; PZ, peripheral zone; Trans., *ERG* gene rearrangement associated with translocation; TZ, transition zone; UZ, undetermined zone; Vol., volume.