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Teaching Case

On Complete Clinical Response of Basal Cell Carcinoma of the Prostate After Definitive Concurrent Chemoradiation

Diego A.S. Toesca, MD,[a,*] Scott M. Cheney, MD,[b] Parminder Singh, MD,[c] Melissa L. Stanton, MD,[d] and William W. Wong, MD[a]

[a]Department of Radiation Oncology, Mayo Clinic, Phoenix, Arizona; [b]Department of Urology, Mayo Clinic, Phoenix, Arizona; [c]Department of Medical Oncology, Mayo Clinic, Phoenix, Arizona; and [d]Department of Pathology, Mayo Clinic, Phoenix, Arizona

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Introduction

Prostate cancer is the most common cancer for men in the United States.[1] Although most cases are composed of epithelial neoplasms, other histologic entities have been identified including neuroendocrine, mesenchymal and hematolymphoid neoplasms. Combined, nonepithelial neoplasms comprise less than 2% of all diagnosed prostate cancer cases.[2,3] Basal cell carcinoma (BCC) is an extremely rare histologic subtype of malignant epithelial prostate neoplasms not associated with prostate-specific antigen (PSA) elevation and is commonly an incidental diagnosis after transurethral resection of the prostate (TURP) in the setting of benign prostatic hyperplasia.[4,5] Because of its rarity, no standard-of-care treatment has been established.

In this report, we present a case of a patient diagnosed with BCC of the prostate with disease involvement into the corpus spongiosum who demonstrated a complete radiographic response after treatment with definitive chemoradiation.

Case Report

A 77-year-old man with a prior history of benign prostatic hyperplasia under medical treatment with oral alpha blocker noticed markedly worsening lower urinary tract symptoms during the previous year. He was referred by his urologist to the Department of Urology at Mayo Clinic Arizona for further evaluation and consideration for minimally invasive prostate enucleation for symptom relief.

On presentation, his PSA was mildly elevated to 7 μg/dL, but with a percent-free PSA of 36%. On digital rectal examination, the prostate was enlarged, without suspicious nodularity. His International Prostate Symptom Score was 16 points (moderate symptom severity). A recent multiparametric magnetic resonance imaging (MRI) of the prostate/pelvis with and without intravenous contrast was notable for an enlarged prostate gland with estimated volume of 189 mL, predominance of multinodular transitional zone, and a calculated Prostate Imaging Reporting & Data System, version 2.1 scoring of 2 or low (clinically significant cancer is unlikely to be present; Fig. 1).

In June of 2022, the patient underwent a holmium laser enucleation of the prostate (HoLEP) with tissue morcellation. Surgical pathology demonstrated 156 g of total tissue removed and identified an infiltrative basal cell neoplasm with a predominant adenoid-cystic pattern, cribriform architecture, intraluminal eosinophilic

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All data relevant to the study are included in the article or uploaded as supplementary information.

*Corresponding author: Diego A.S. Toesca, MD; Email: santostoesca.diegoaugusto@mayo.edu

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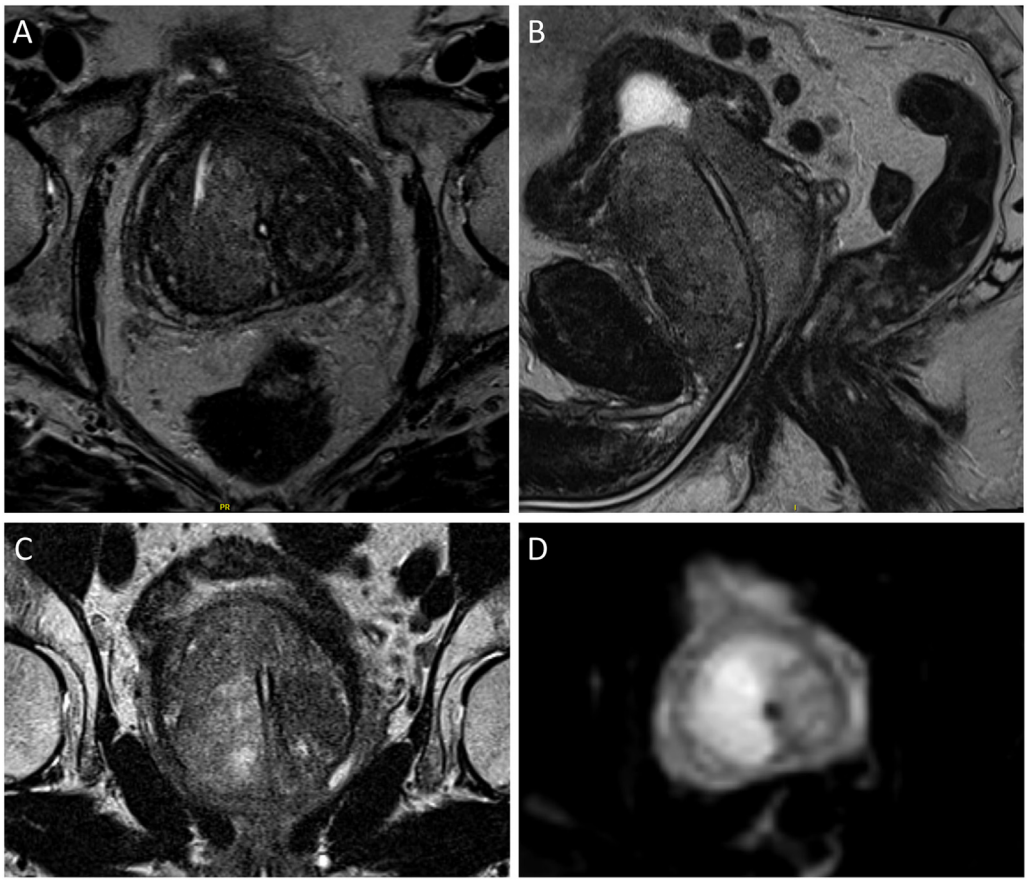

Figure 1 Magnetic resonance of the prostate before holmium laser enucleation of the prostate. (A) Axial T2 TSE sequence, (B) sagittal T2 TSE sequence, (C) coronal T2 TSE sequence, and (D) axial diffusion sequence.

material, and myxoid stroma. Some fragments demonstrated smooth muscle and loose fibroconnective tissue, suggesting extension into periprostatic tissue. One fragment showed urothelium, suspicious for bladder neck involvement. No perineural invasion or necrosis was seen in the tumor and no conventional prostatic adenocarcinoma was present. Immunohistochemical stains showed the tumor cells to be positive for basal cell markers (PIN multiplex) and bcl-2. NKX3.1 immunohistochemistry showed rare positive cells. Ki67 showed an increased proliferative index (>30%). Immunohistochemical stains for synaptophysin and chromogranin were negative. Final diagnosis was consistent with BCC, involving >90% of the submitted tissue (Fig. 2).

Subsequently, MRI of the pelvis with and without intravenous contrast was performed in August 2022 and showed diffuse heterogeneous T2 hyperintense signal with associated diffusion restriction and postcontrast enhancement throughout the residual prostate, extending along the posterior and inferior aspects of the pubic symphysis. Also seen was a focal hyperenhancement within the corpus spongiosum extending for 3.1 cm on the left and 1.8 cm on the right, with no associated diffusion restriction, separate from the prostatic abnormal soft tissue (Fig. 3). ^{18}F-fluorodeoxyglucose (FDG) position emission tomography (PET) demonstrated postsurgical changes of the prostate status post HoLEP, moderate heterogeneous tracer uptake involving the medial aspect of the left and to a lesser extent right seminal vesicles measuring approximately 2.2 × 2.0 cm and 1.8 × 1.4 cm, respectively, with a maximum standard uptake value (SUVmax) of 5.4, considered nonspecific. Of note, also observed was an area of intense focal tracer uptake along the inferior aspect of the root of the penis, measuring 2.1 × 1.6 cm with a SUVmax of 13. No PET evidence of distant tracer avid metastatic disease was observed (Fig. 4A and B).

The focus of nodular enhancement at the penile root was not biopsied but considered highly suspicious for malignancy because of the similar imaging characteristics to the primary prostate lesion on MRI and its hypermetabolism on FDG-PET. Hence, after multidisciplinary tumor board discussion, external beam radiation therapy (EBRT) was recommended in lieu of RARP. Between November 2022 and January 2023, the

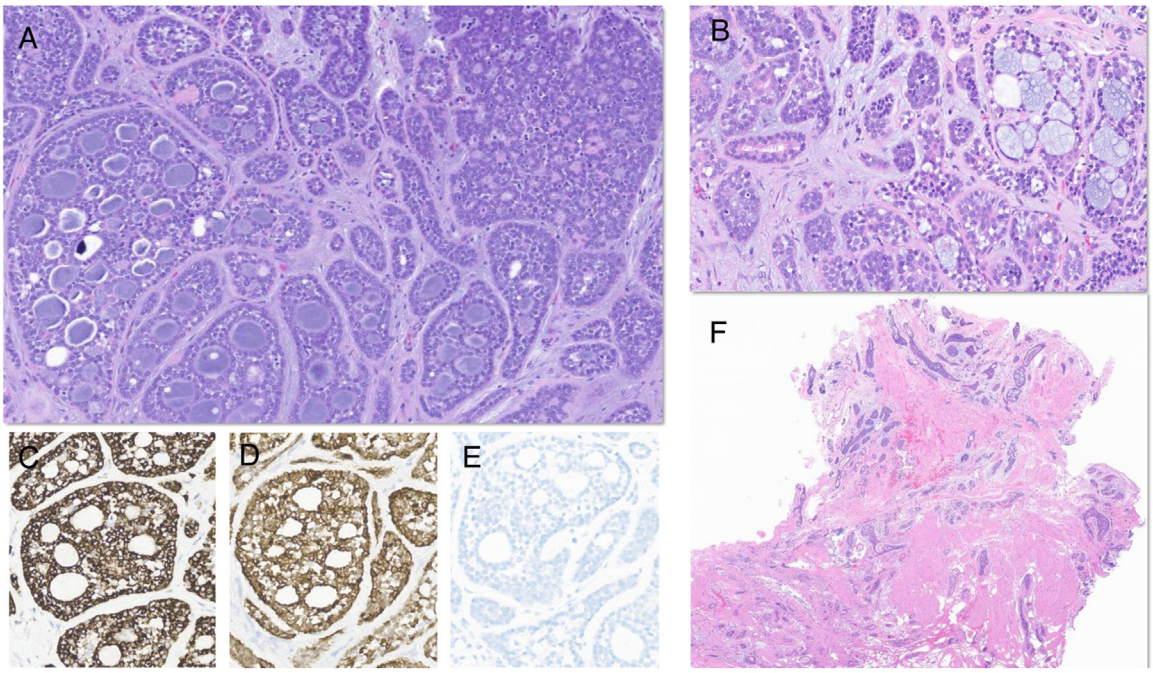

Figure 2 Histologic features of basal cell carcinoma of the prostate. (A) Cribriform architecture with peripheral palisading, rigid circular spaces containing intraluminal eosinophilic and basophilic material and a background myxoid stroma, imparting an appearance similar to adenoid-cystic carcinoma of the salivary gland (hematoxylin and eosin [H&E], 20 ×). (B) Small nests and tubules embedded in a myxoid stroma (H&E, 20 ×). (C-E) Immunohistochemical stains: (C) positive bcl- 2, (D) positive p63 and high molecular weight keratin, the basal cell markers in PIN3 multiplex, (E) negative NKX3.1, a transcription factor marker for androgen-derived prostate tissue (IHC, 25 ×), (F), tumor nests haphazardly infiltrating bundles of smooth muscle with associated desmoplasia, suspicious for bladder neck invasion (H&E 10 ×).

patient received EBRT to the prostate and penile lesion using intensity modulated radiation therapy (IMRT), with concurrent weekly cisplatin at a dose of 40 mg/m^2. The choice for using a platin-based chemotherapy regimen was based on extrapolation from the effect of these agents on advanced cutaneous basal cell carcinomas. The diagnostic FDG PET and MRI of the pelvis were coregistered with treatment simulation CT scan to assist with target contouring. A high-dose clinical target volume was created that included the prostate, external urethral sphincter, proximal seminal vesicles, retropubic abnormal soft tissue, and the penile root. A low-dose clinical target volume was designed that included the superior seminal vesicles beyond the aforementioned structures. Isometric expansions of 6 mm from the CTVs were used to create the high and low-dose planning target volumes, with PTVlow receiving a total of 63 Gy (biologically effective dose of 74 Gy for an α/β of 10), and the PTVhigh to 72 Gy (biologically effective dose of 86.4 Gy for an α/β of 10), both in 36 daily fractions (Fig. 5). Radiation treatments were delivered with daily image guidance via kV cone beam CT for soft tissue alignment.

Concurrent chemoradiation was well tolerated. No major toxicity was reported. The patient experienced only minimal treatment-related side effects, including grade 1 fatigue, and grade 1 noninfective cystitis (minimal increase in nocturia), both during treatment and that resolved with treatment completion. Follow-up with restaging FDG PET/CT at 6 months showed nonspecific mild diffuse uptake at the residual prostate and seminal vesicles with SUVmax of 4.8, nonspecific, and complete resolution of the previously seen hypermetabolic area at the root of the penis suggesting a complete radiographic response (Fig. 4C and D). His posttreatment PSA at 6-months posttreatment was 0.7 ng/dL. The patient will continue with follow-ups with repeat imaging (MRI pelvis or FDG PET/CT) every 6 months up to 2 years, and subsequently at yearly intervals.

Discussion

Basal cell carcinoma of the prostate is a rare subtype of prostate cancer. These tumors are not associated with PSA elevation or prostate specific acid phosphatase levels.

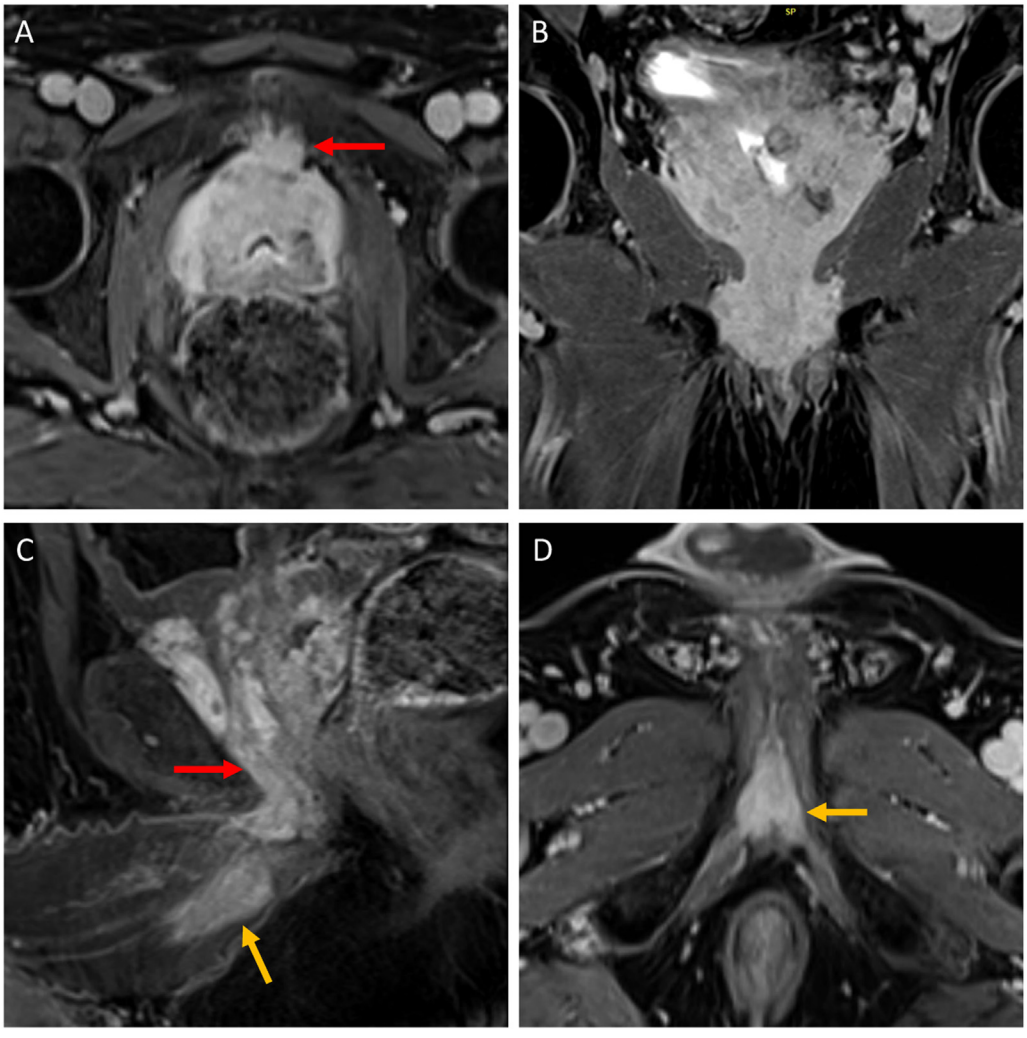

Figure 3 Magnetic resonance of the prostate post holmium laser enucleation of the prostate. (A) Axial T1 postcontrast sequence at prostate level, (B) coronal T1 postcontrast sequence, (C) sagittal T1 postcontrast sequence, and (D) axial T1 postcontrast sequence at penile bulb level.
Red arrows = abnormal enhancing soft tissue at the prostate; yellow arrows = abnormal enhancing soft tissue at the corpus spongiosum of the penis.

As a result, screening PSA is not useful for early diagnosis of the disease. It is often found incidentally during workup and treatment for obstructive urinary symptoms or hematuria.[6] In our case, the PSA level was 7 ng/dL, with a percent-free PSA of 36%, which was consistent with benign prostatic hyperplasia and a low suspicion of prostate cancer. The diagnosis of BCC was made incidentally from tissue obtained from HoLEP for the treatment of bladder outlet obstruction.

BCC can be subclassified histologically into 2 variants, adenoid-cystic, which resembles salivary gland tumors, and basaloid when they lack that histologic appearance. These tumors can present with varying morphologic patterns such as adenoid-cystic-like, small solid nests with peripheral palisading, basal cell hyperplasia-like, small tubules or large solid nests with or without necrosis.[7] More commonly, more than one pattern is present within the tumor, frequently associated with a desmoplastic stromal response, useful to distinguish BCC from basal cell hyperplasia.[8,9] In contrast to acinar adenocarcinoma, BCC shows little or no androgen receptor expression. Immunohistochemistry shows diffuse positivity for bcl2 in most cases, associated with basal cell markers, such as high molecular weight cytokeratin and p63, while lacking immunoreactivity for PSA.[10] High Ki67, which ranges from 2% to 80% in the literature, as well as perineural

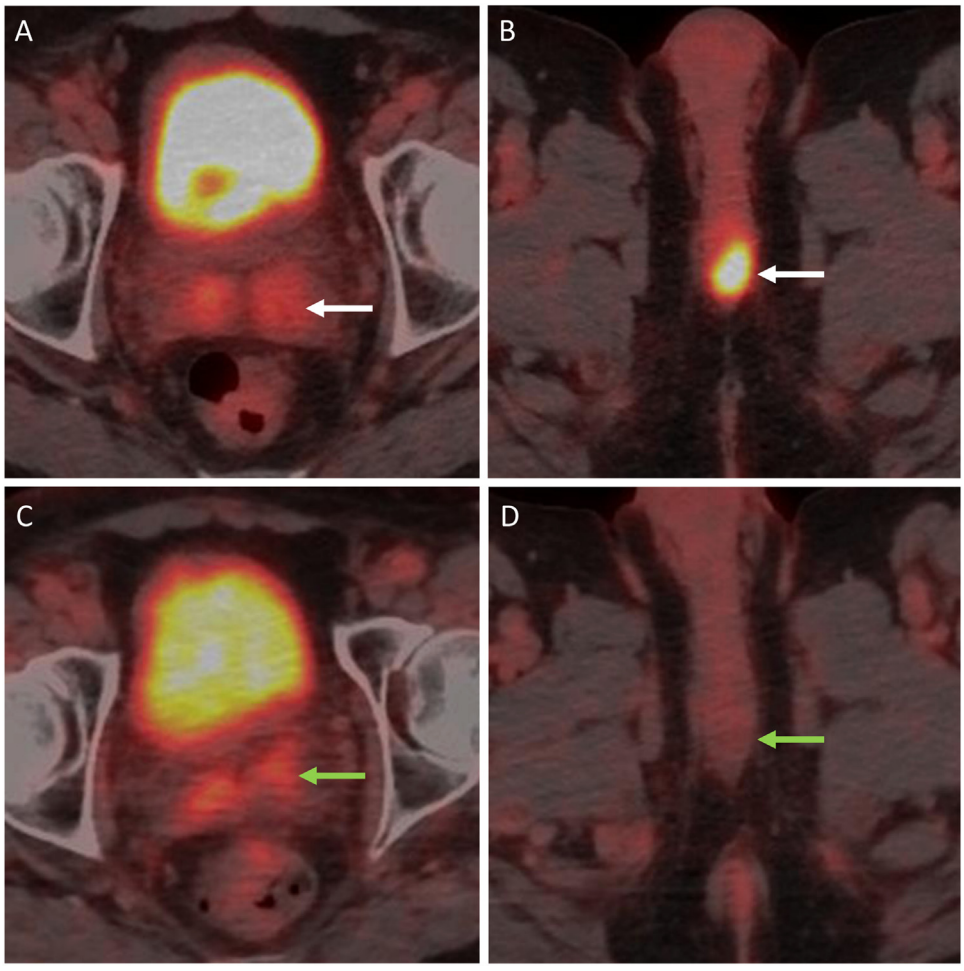

Figure 4 ^{18}F-fluorodeoxyglucose position emission tomography showing: (A) axial view at the level of the seminal vesicles base before chemoradiation, (B) axial view at the level of the penile bulb before EBRT, (C) axial view at the level of the seminal vesicles base 6 months after chemoradiation, and (D) axial view at the level of the penile bulb 6 months after chemoradiation.

invasion and lymphovascular invasion are helpful markers to differentiate BCC from florid basal cell hyperplasia.[9] Previous reports have shown mutations in the MYB proto-oncogene, EGFR, HER2-neu and PTEN genes.[11-13]

The clinical behavior of BCC is variable, and although most reported cases are indolent, aggressive behavior is possible, especially among those with adenoid-cystic variant and high Ki67.[7] In the present case report, the tumor showed signs of local aggressiveness with periprostatic extension and high Ki67, as well as the presence of soft tissue extension into the penis.

Because of its rarity, no high-level evidence exists to define the optimal treatment strategy. A recent literature review identified a total of 106 patients who were treated for BCC of the prostate, showing significant variability in management approaches.[14] Radical prostatectomy was reported in up to a third of cases while some patients were treated solely with TURP for symptomatic control. Adjuvant EBRT was used in about 10% of the cases, with doses of up to 66 Gy delivered with conventionally fractionated regimens. Cases of patients treated with definitive EBRT, with or without chemotherapy, were fewer (8%) with doses ranging from 45 to 70 Gy. Concurrent radiation and chemotherapy appear to be an effective treatment as illustrated in a recent case report by Ridai et al. The authors described a patient incidentally diagnosed with BCC after TURP who was treated with definitive EBRT to 70 Gy in 35 fractions using IMRT, and concurrent weekly cisplatin.[15] The authors included elective pelvic nodal irradiation to a lower dose of 46 Gy because the tumor invaded into the seminal vesicles.

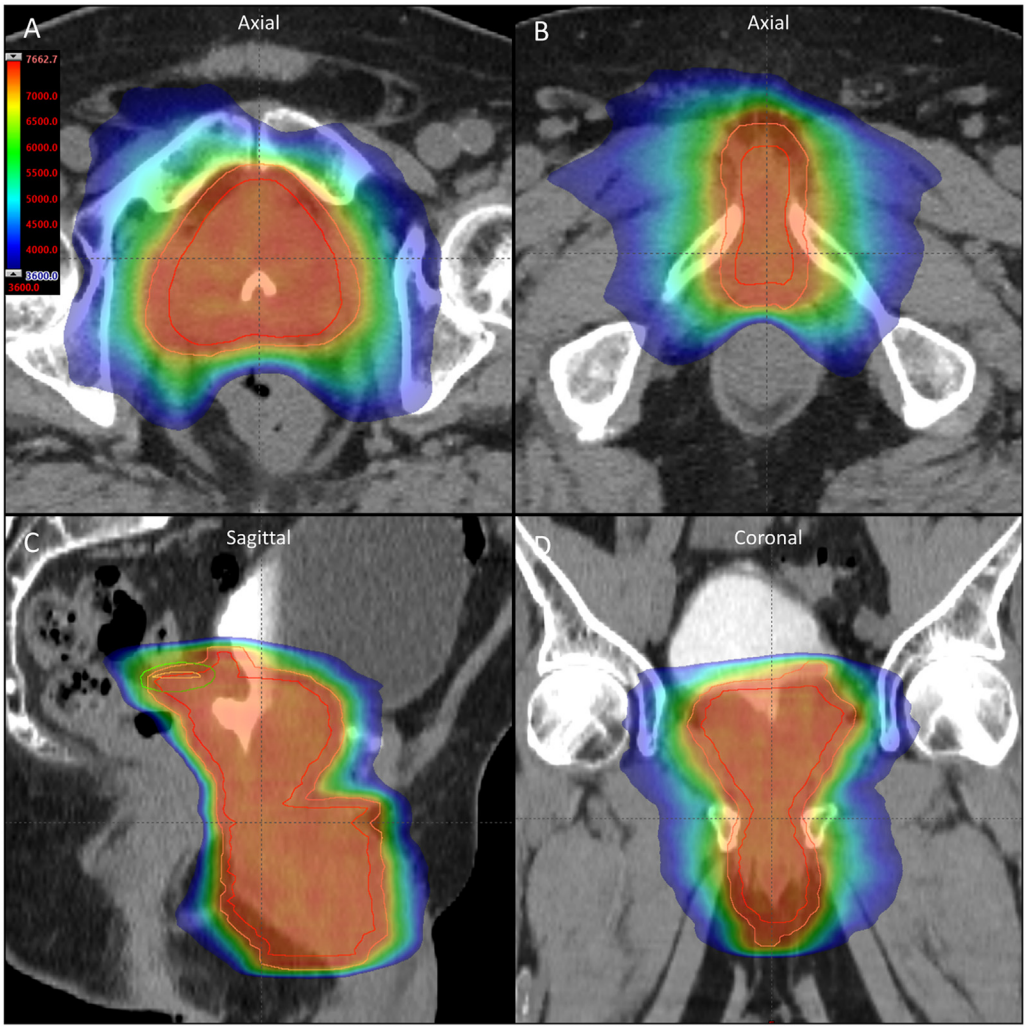

Figure 5 Radiation therapy plan with total dose shown in color wash: (A) axial view at the level of prostate, (B) axial view at the level of the penile root, (C) sagittal view, and (D) coronal view.

At 1.5 years of follow-up, this patient continued to show local disease control in the pelvis but eventually developed biopsy-confirmed brain metastasis. In our case, excellent treatment response was seen with similar chemoradiation regimen of 72 Gy EBRT and weekly cisplatin. We opted not to treat the pelvic lymph nodes electively considering the lack of evidence and the absence of suspicious nodal hypermetabolic activity on FDG PET/CT. The risk of lymph node involvement is not well studied for these tumors, and further clinical evidence would be extremely useful to answer that question. Longer follow-up will be necessary to better assess the effect of local disease control on overall and metastasis-free survival. We propose a management nomogram based on our recommendations for different clinical scenarios involving diagnosis of basal cell carcinoma of the prostate (Fig. 6). This nomogram is not based on high-level clinical evidence, but rather clinical judgment supported by limited published experience. Because of the rarity of this pathology, future collective efforts using multiinstitutional data are warranted to improve the strength of available evidence and serve as guidance for future management.

Conclusion

BCC of prostate is a rare pathologic variant of prostate cancer. We have reported a case of complete clinical response achieved with EBRT and concurrent weekly cisplatin. A multiinstitutional database that

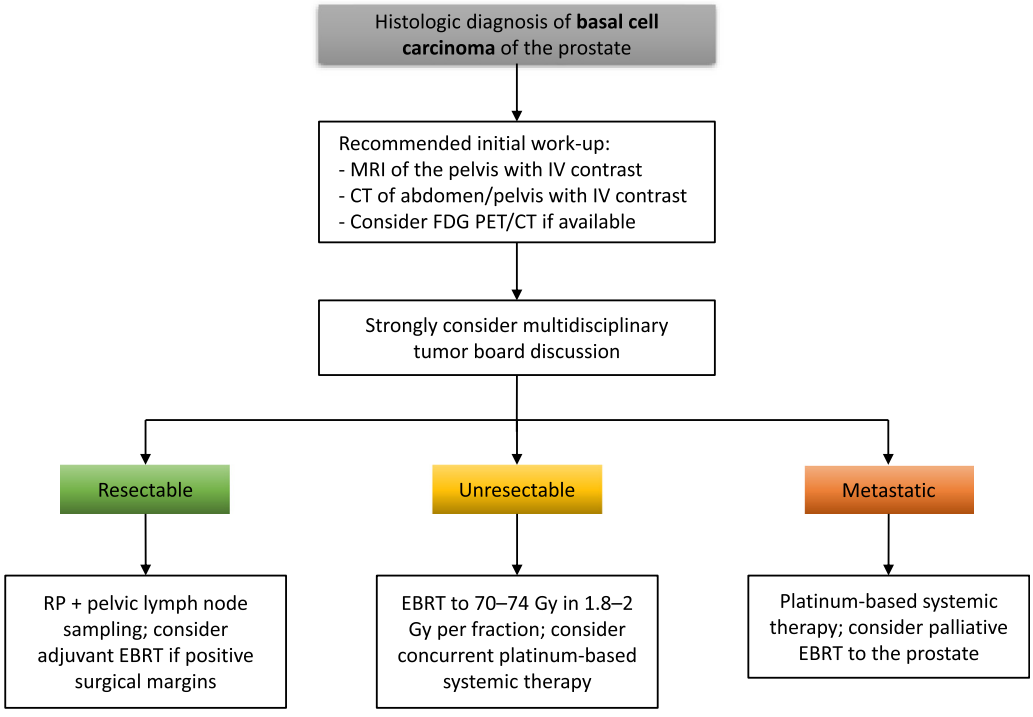

Figure 6 Proposed nomogram for management of patients who received a diagnosis of basal cell carcinoma of the prostate. *Abbreviations:* EBRT = external beam radiation therapy; RP = radical prostatectomy.

includes a larger number of cases would be needed to provide more information on the natural history and guidance for management of this disease.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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