ORAL METASTASIS TO THE ORAL CAVITY - AN EMERGING PROSTATE CANCER RISK FACTOR: A REVIEW

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ABSTRACT

Metastatic tumors involving the jaw constitute a rare occurrence, encompassing approximately 1% to 4% of all oral malignancies resulting from distant primary tumors. Among the leading sources of metastatic tumors to the oral or maxillofacial region are breast, lung, prostate, kidney, bone, colon, rectum, thyroid, stomach, testis, bladder, ovary, and cervix cancers. Oral cavity metastatic tumors are infrequent, comprising approximately 1% of all oral malignancies. Remarkably, in 25% of cases, the presence of oral metastasis serves as the initial indicator of metastatic progression, while in 23%, it constitutes the earliest discernible evidence of malignancy spreading from its primary origin. Prostate cancer typically originates from the basal cells within the prostate, and it ranks as the 6th most common cause of cancer-related mortality among males worldwide. Prostate cancer is indeed a significant health concern for men, its prevalence and impact on male health underscore the importance of regular screening, early detection, and appropriate medical management to improve outcomes and reduce mortality rates. In our review, we explore different risk factors and predisposing conditions, as well as the primary pathway through which prostate carcinoma metastasizes to the oral cavity.

KEYWORDS

Metastasis, Prostate cancer, Oral cavity, Hematogenous, Venous, Lymphatic

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INTRODUCTION

When assessing oral tumors, it's noteworthy that a mere 1% to 3% of oral malignancies originate from distant primary sites. These metastatic tumors most commonly stem from various sources, with different prevalence in females and males. In females, they predominantly arise from the breast, adrenal gland, colorectal system, genital organs, and thyroid gland. In males, the leading sources include the lung, prostate, bone, and adrenal gland.[1, 2]

Metastasis to the jaw is relatively rare when compared to metastasis to other bones in the body, constituting only a small fraction of such cases. Specifically, it accounts for approximately 1% of all malignant neoplasms affecting the oral region. Research conducted by Shen et al indicates that within the category of oral and maxillofacial metastases, those originating from prostate cancer represent approximately 6.2% of the total cases.[3] Due to the rarity of cases involving oral cavity metastases from the prostate gland, it becomes particularly crucial to establish an accurate diagnosis and determine the appropriate treatment approach.[4]

In our comprehensive review, we have highlighted a range of factors that elevate the risk of metastasis and have presented theoretical pathways that elucidate how prostate carcinoma might disseminate to different regions of the body, including the oral cavity.

Prostate cancer is a form of cancer that develops within the prostate gland, an integral component of the male reproductive system. The prostate gland is a small, walnut-shaped gland responsible for producing seminal fluid, essential for nourishing and facilitating the transportation of sperm. It is situated just beneath the bladder and in front of the rectum.[5] Prostate cancer is characterized as a slowly progressing malignancy that originates from the basal cells within the prostate,[6] and it ranks as the 6th most common cause of cancer-related mortality among males worldwide.[7]

Prostate cancer is a prevalent malignancy in men, typically characterized by its propensity to metastasize to bones and regional lymph nodes. While distant metastasis is common, metastasis to the oral cavity remains a rare and intriguing clinical phenomenon. Within the maxillofacial region, prostate carcinomas exhibit a preference for metastasizing to the jawbone. Notably, in men, approximately 11% of jawbone metastases have their origin in the prostate gland, whereas only 1.5% occur in the soft tissues. Among the areas within the jaw, the mandible is the most commonly affected site for oral metastasis, accounting for 35.6% of cases. Specifically, the molar and premolar region is the most frequently involved, representing 53.0% of cases, followed by the ascending ramus (31.6%), mandibular angle (17.8%), condyle (15.8%), and the mental region (6.1%).[3]

In its early stages, prostate cancer often does not cause noticeable symptoms. However, as it progresses, some possible symptoms may include frequent urination, difficulty starting or stopping urination, weak urine flow, blood in the urine or semen, erectile dysfunction, and pain in the hips, back, or pelvis as the cancer progresses.[8] The primary symptoms produced by prostate cancer (Figure 1) are outlined in Flowchart 1. According to Hirshberg et al,[9] symptoms linked to metastases encompass instant swelling, pain, and paresthesia. These particular symptoms can serve as key indicators of jaw metastases.

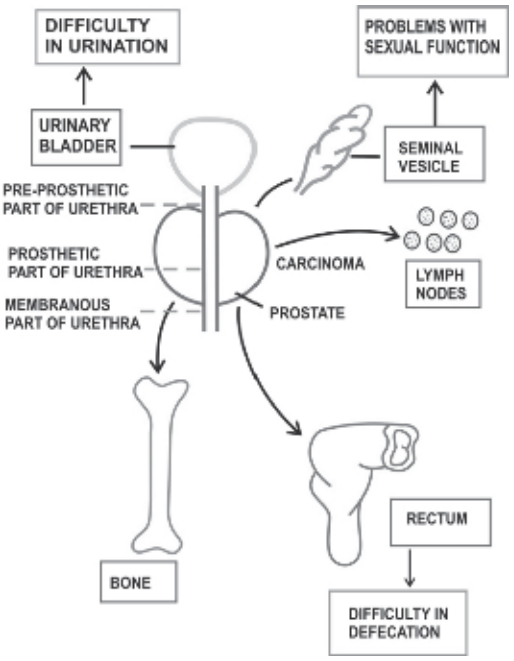
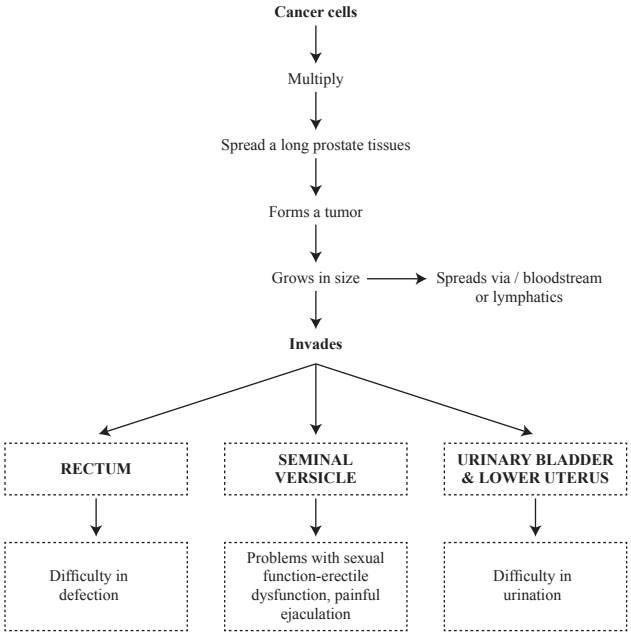


Figure 1. The primary symptoms produced by prostate cancer



Flowchart 1. Primary symptoms produced by prostate cancer

Prostate cancer is typically diagnosed through a combination of tests, including a digital rectal exam (DRE), a blood test measuring prostate-specific antigen (PSA) levels, and a transrectal ultrasound (TRUS) guided biopsy to confirm the presence of cancer cells. Imaging modalities play a crucial role in diagnosing, staging, and monitoring prostate cancer. Several imaging modalities commonly used are: Multiparametric Magnetic Resonance Imaging (mpMRI),

Computed Tomography (CT) Scan, Bone Scans, ProstaScint Scan (Monoclonal Antibody Imaging) and Positron Emission Tomography (PET) Imaging.[10]

The precise origin of prostate cancer remains a subject of ongoing investigation.[11] Several factors have been associated with an increased risk of prostate cancer, including age, race, a family history of prostate cancer among first-degree relatives,[12] environmental influences and hormonal levels.[7, 13] These risk factors are depicted in figure 2.

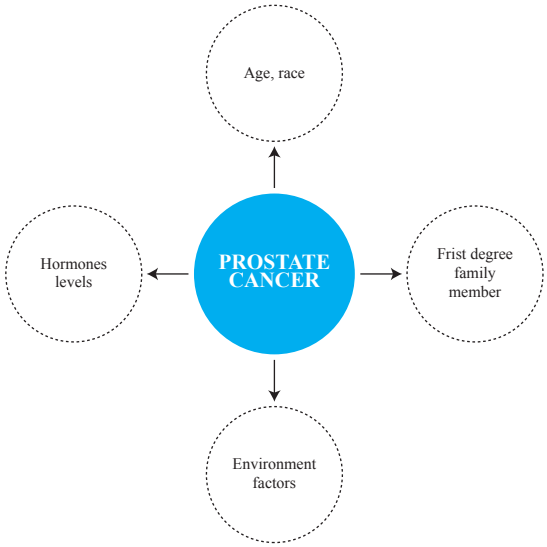


Figure 2. Risk factors for prostate cancer

Predisposing factors that can increase susceptibility to prostate cancer and may have a significant impact include hypertension,[14] a sedentary lifestyle, insufficient vitamin D levels in the bloodstream, excessive multivitamin consumption (more than 7 times per week), folic acid supplementation, diet abundant in lycopenes, vitamin A, vitamin E, selenium, and soy-based products, elevated levels of testosterone, obesity[15-17] and sexually transmitted infections (such as Chlamydia, gonorrhea, and syphilis). These contributing factors are illustrated in figure 3.

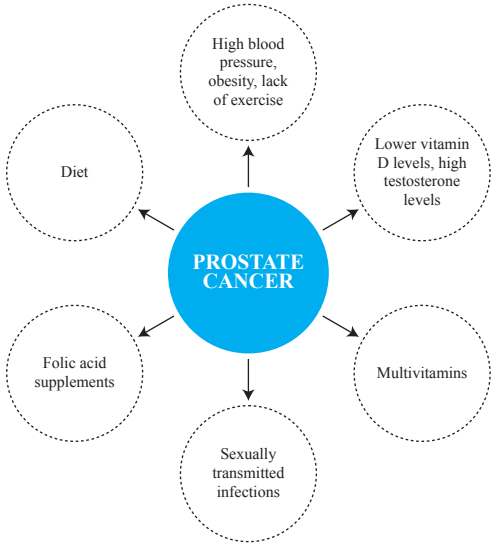


Figure 3. Predisposing factors for prostate cancer

Prostate cancer has been associated with numerous genes, indicating its genetic complexity. Mutations in BRCA1 and BRCA2,[18] known for their significant roles in breast and ovarian cancer, are also believed to contribute to prostate cancer risk. Additionally, other genes implicated in prostate cancer include Hereditary Prostate Cancer Gene 1 (HPC1), as well as genes related to androgen and vitamin D receptors.[19] The disease's progression involves the loss of cancer suppressor genes in its early stages, while the loss of tumor suppressor genes like p53 occurs during its advanced spread. Other tumor suppressor genes involved in prostate cancer include PTEN, RB1, KAI-1, along with the loss of E-Cadherin and CD44.[20, 21] Recent genomic studies have identified overexpression of the transcription factor EZH2 in aggressive and metastatic prostate cancer.[22] Recent advancements in prostate cancer diagnosis and prognosis have introduced several innovative markers and tests. These include diagnostic markers such as 4Kscore®, [-2] proPSA, Prostate Health Index, SelectMDx®, ConfirmMDx®, Progensa® Prostate Cancer Antigen 3, Mi-Prostate Score, ExoDx™ Prostate Test, the Stockholm3 test, and ERSPC risk calculators. Additionally, there are prognostic markers like OncotypeDX® Genomic Prostate Score, Prolaris®, Decipher®, and ProMark®.[23] These markers and tests offer healthcare professionals valuable tools for more accurate diagnosis, risk assessment, and treatment planning in prostate cancer cases. Figure 4 illustrates the various genes associated with prostate cancer.

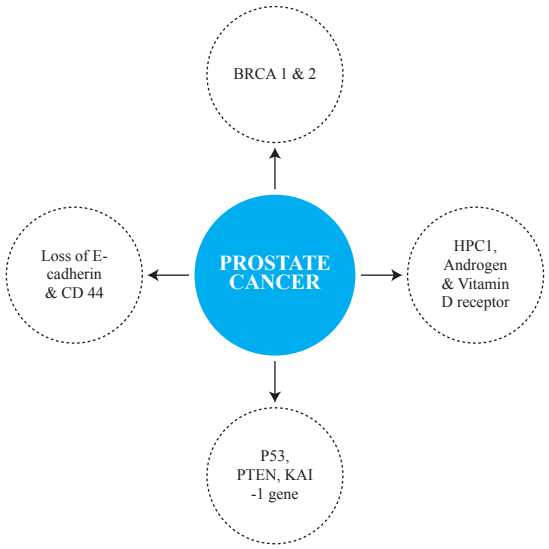


Figure 4. The various genes associated with prostate cancer

Metastasis of prostate cancer occurs when cancer cells break away from the primary tumor in the prostate and enter the bloodstream or lymphatic system, allowing them to travel to distant organs and tissues. Prostate cancer most commonly metastasizes to the bones, particularly the spine, pelvis, and long bones, but it can also spread to lymph nodes, liver, lungs, and other organs. Prostate cancer metastasizes to the bones, primarily the vertebral column and pelvis, through valveless connections between the prostate venous plexus (PVP) and the internal vertebral venous plexus.[24] Recent research indicates that urinary difficulties can raise pressure within the prostate venous plexus. As these plexuses lack valves, blood can flow in a retrograde direction, eventually

entering the vertebral venous plexus via the lumbar vein, thus allowing malignant cells to become lodged in the vertebral column.[25] Figure 5 provides an illustration of the venous drainage pathway.

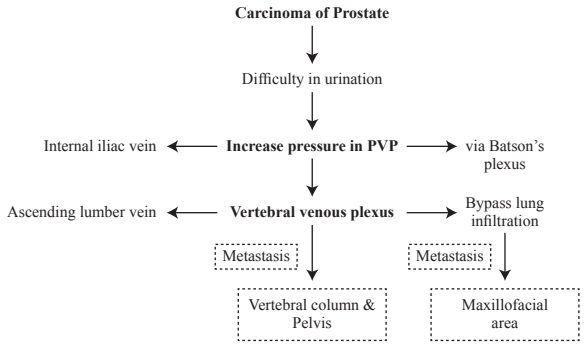


Figure 5. Venous metastatic pathway for prostate cancer

Prostate cancer has a predilection for metastasizing to specific bone sites, with the vertebrae being the most favored, followed by the pelvis, ribs, and the proximal part of the femur. Bone pain, as depicted in figure 6, is the primary symptom associated with cancer metastasis to the bones. When prostate cancer spreads to the spine, it can lead to a critical complication known as spinal cord compression. This can result in symptoms such as leg weakness, as well as urinary and fecal incontinence due to the compression and impairment of the spinal cord's function.[26]

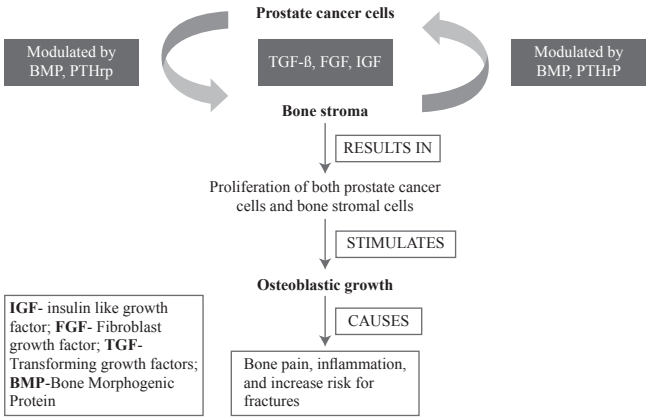


Figure 6. Bone pain caused by prostate cancer metastasis to the bone

Prostate cancer cells can spread to the lymph nodes located around the iliac and common iliac arteries, as well as the aorta, through the lymphatic vessels in the pelvis.[27-28] This lymphatic spread is illustrated in figure 7 and is an important aspect of cancer staging and treatment planning in prostate cancer cases. The presence of cancer in these distant lymph nodes can indicate a more advanced stage of the disease and may influence treatment decisions.

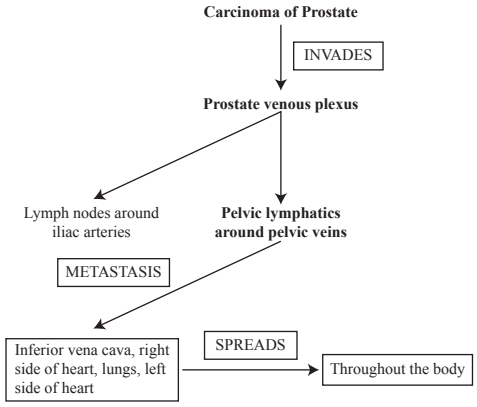


Figure 7. Lymphatic metastatic pathway for prostate cancer

CONCLUSION

This comprehensive review underscores the importance of considering prostate cancer metastasis as a potential etiology in patients presenting with oral cavity lesions, particularly in the context of a known history of prostate cancer. Comprehensive understanding of the routes of metastasis and the involvement of specific genes and factors is essential for early detection, accurate staging, effective management of prostate cancer and enhancing patients' overall well-being. While prevention strategies are not foolproof, maintaining a healthy lifestyle with a balanced diet, regular exercise, and not smoking may reduce the risk of developing prostate cancer. Further research is needed to elucidate the mechanisms underlying this rare metastatic pattern and to optimize treatment strategies.

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