CLINICAL VIGNETTE

Treatment of Oligometastatic Prostate Cancer

Mahshid Mosallaei-Benjamin, MD and Joshua Rosenberg, MD

Increasing understanding of molecular biology of cancer metastases has not improved understanding the epidemiology of metastases compared to primary cancers. Population based data on metastatic patterns of tumors are seldom included in cancer registries. However, clinicians are often challenged to treat patients presenting with metastatic disease that is limited in both the amount of tumor and extent of metastatic sites. The need to identify the tumor tissue of origin increases the complexity in formulating treatment. It is intuitive that patients with lower disease burden should have better prognosis, but metastatic treatment may not vary by the extent of metastatic disease. We present a patient with oligometastatic tumor and the proposed treatment.

An 89-year-old male developed persistent dry cough, shortness of breath with exertion, and increased urinary frequency over the previous four months. He also lost five pounds, without change in appetite. His primary care doctor obtained a chest x-ray that revealed multiple bilateral lung nodules concerning for metastatic disease. Chest CT scan confirmed bilateral lung nodules concerning for metastatic disease.

The patient's past medical history includes hypertension, basal cell cancers, and benign prostatic hypertrophy with prior TURP. His PSA has progressively increased more than twelve years ago. PSA was 25 and subsequent TURP did not show invasive prostate cancer. PSA about a year ago was elevated at 82. CT guided biopsy of right lower lobe lung nodule was consistent with adenocarcinoma, most compatible with prostatic origin.

A PET CT for staging revealed more than 20 solid pulmonary nodules with mild to moderate (SUV max 5.2) FDG uptake. Some had some small areas of cavitation and increased size. A right lower lobe nodule increased to 18 x 14 mm (SUV max 2.5) from 16 x 14 mm.

The prostate showed heterogeneous increased enhancement and nodularity. These were areas of moderate FDG uptake (up to SUV max 4.4) in the bilateral apex, with ill-defined enhancing tissue extending into the right greater than left seminal vesicle. There is a central TURP defect with median lobe hypertrophy and enhancing nodules impressing on the bladder base.

Other findings included a large hemangioma of the T11 vertebral body with peri centimeter sclerotic focus demonstrating moderate FDG uptake (SUV max 4.4). Additional scattered sclerotic foci in this vertebral body and pelvis were without significant uptake and may represent bone islands.

A Cancer Type ID test was ordered to confirm diagnosis of prostate cancer due to a paucity of other sites of disease detected on PET scan. This assay uses real time PCR to measure the expression of 92 genes in a tumor sample and classifies the tumor by matching the gene expression pattern from a database of over 2000 known tumor types and subtypes. The assay returned with 96% certainty that the tumor was of prostatic origin.

Treatment options were discussed with the patient. Due to his age and lack of significant symptoms, he was started on Androgen deprivation therapy. After 5 months of treatment, his PSA declined to 2.3 from 107.0. Follow up PET scan 3 months after initiation of treatment showed: interval decrease FDG uptake throughout prostate gland, interval decrease size and FDG uptake of bilateral metastatic pulmonary nodules, and no new sites of disease.

Discussion

This patient illustrates several important points. Patterns of metastatic disease can be confusing and misleading. Our patient was initially referred to pulmonology for his symptomatic cough, which resolved prior to any treatment. However, a chest scan was obtained to evaluate the cough. This revealed pulmonary modules which were initially thought to be advanced stage lung cancer in a patient with previous smoking.

A 2018 study using the Swedish Cancer Registry described metastatic pathways in 14 common primary cancers to 12 specific metastatic sites. In males, colorectal cancer was the primary source of lung, peritoneal and liver metastases. Prostate cancer was the primary source of most bone metastases at every age, but mostly ages over 70. The registry showed 89% of prostate cancer patients had bone metastases. The next most common metastatic site was the liver.[1] Our patient did not have metastatic disease to the bone and had very little radiographic evidence of prostate abnormality. The gene expression assay was obtained to confirm that the lung metastases were of prostate origin.

Multiple commercial assays are now available for tumor of origin identification based on a small amount of tissue. At this

time, expression profiling assays are often considered investigational and not covered by health insurances.

Traditional treatment for metastatic prostate cancer involves androgen deprivation without a focus on treating the primary tumor. Metastatic tumor is considered a systemic rather than a localized disease. Men with newly diagnosed Prostate cancer with distant metastases have a 5-year survival rate of 31%.[2]

The definition of Oligometastatic disease (OMD) is controversial. It is generally thought to be an intermediate state between localized and aggressive metastatic prostate cancer involving fewer than 3-5 metastatic lesions.[3] Due to diagnostic improvements, OMD is being diagnosed with greater frequency. Retrospective data suggests that aggressive treatment of Oligometastatic disease including radical prostatectomy, nodal dissection, and metastasis directed radiotherapy can improve survival, delay development of castration resistance, with the potential for cure.[4]

Support for aggressive treatment of oligometastatic prostate cancer has been seen in other solid cancers. These include:

1. Improved survival after resection of liver metastases in advanced stage colon cancer with liver metastases.[5]
2. Improved survival after resection of pulmonary metastases in patients with metastatic sarcoma, germ cell tumor and melanoma.[6]
3. Improved survival after resection of solitary metastases to the brain, adrenal glands or lung in patients with metastatic lung cancer.[7]

In the STAMPEDE (arm H) trial, 2061 patients with de novo metastatic Prostate Ca were randomized to androgen deprivation therapy (ADT) with or without Radiation therapy (RT) to the prostate. They reported no difference in the primary endpoint of overall survival at 3 years. However, the pre-specified analysis of the group with low metastatic burden (defined as < 4 bone metastases) RT improved 3-year survival. OS was 81% vs 73%, (95% CI 0.68–0.84). This extrapolates to a 27 percent reduction in death with the addition of primary radiation therapy to the prostate.[8]

Updated data after median follow-up of 61 months and 1183 events was published in 2022. Prostate RT improved overall survival in patients with low metastatic burden. There were 202 deaths in the ADT alone group versus 156 in ADT+RT group, HR 0.64, 95% CI 0.52–0.79). Longer follow up showed a 36 percent reduction in death with primary radiation therapy to the prostate.[9]

Additional trials are assessing the benefit of total eradication therapy in men with Oligometastatic prostate cancer. One small study of 12 patients chemohormonal therapy, followed by radical prostatectomy, adjuvant radiation (RT) to prostate bed/pelvis, stereotactic body radiation therapy (SBRT) to oligometastases, and adjuvant hormonal therapy (HT). Overall survival was 12/12 (100%). PSA's remained undetectable in all 12 at year one, 10/12 (83%) at year two and 8/12 (67%) at year 3. They concluded that total eradication of tumor was safe with minimal additive toxicities and may extend the interval of undetectable PSA.[10]

Increased understanding of the molecular biology of both the original tumor and associated metastatic disease will allow additional treatments that improve survival of patients with advanced stage tumors. Many treatments may have minimal side effects based on current clinical trials. Our patient has tolerated androgen deprivation therapy well with no associated side effects. Due to the limited extent of his metastatic disease, he may be offered radiation to the prostate gland/seminal vesicle to potentially improve survival and decrease risk of developing hormone resistant prostate cancer.

REFERENCES

1. **Riihimäki M, Thomsen H, Sundquist K, Sundquist J, Hemminki K**. Clinical landscape of cancer metastases. *Cancer Med*. 2018 Nov;7(11):5534-5542. doi: 10.1002/cam4.1697. Epub 2018 Oct 16. PMID: 30328287; PMCID: PMC6246954.
2. NIH National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Prostate Cancer. [Internet] Available at: https://seer.cancer.gov/statfacts/html/prost.html.
3. **Ahmed KA, Barney BM, Davis BJ, Park SS, Kwon ED, Olivier KR**. Stereotactic body radiation therapy in the treatment of oligometastatic prostate cancer. *Front Oncol*. 2013 Jan 22;2:215. doi: 10.3389/fonc.2012.00215. PMID: 23346551; PMCID: PMC3551203.
4. **Tosoian JJ, Gorin MA, Ross AE, Pienta KJ, Tran PT, Schaeffer EM**. Oligometastatic prostate cancer: definitions, clinical outcomes, and treatment considerations. *Nat Rev Urol*. 2017 Jan;14(1):15-25. doi: 10.1038/nrurol.2016.175. Epub 2016 Oct 11. PMID: 27725639; PMCID: PMC5808411.
5. **Fong Y, Cohen AM, Fortner JG, Enker WE, Turnbull AD, Coit DG, Marrero AM, Prasad M, Blumgart LH, Brennan MF**. Liver resection for colorectal metastases. *J Clin Oncol*. 1997 Mar;15(3):938-46. doi: 10.1200/JCO.1997.15.3.938. PMID: 9060531.
6. **Pastorino U, Buyse M, Friedel G, Ginsberg RJ, Girard P, Goldstraw P, Johnston M, McCormack P, Pass H, Putnam JB Jr; International Registry of Lung Metastases**. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. *J Thorac Cardiovasc Surg*. 1997 Jan;113(1):37-49. doi: 10.1016/s0022-5223(97)70397-0. PMID: 9011700.
7. **Peters S, Adjei AA, Gridelli C, Reck M, Kerr K, Felip E; ESMO Guidelines Working Group**. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012 Oct;23 Suppl 7:vii56-64. doi: 10.1093/annonc/mds226. PMID: 22997455.
8. **Parker CC, James ND, Brawley CD, Clarke NW, Hoyle AP, Ali A, Ritchie AWS, Attard G, Chowdhury S, Cross**

W, Dearnaley DP, Gillessen S, Gilson C, Jones RJ, Langley RE, Malik ZI, Mason MD, Matheson D, Millman R, Russell JM, Thalmann GN, Amos CL, Alonzi R, Bahl A, Birtle A, Din O, Douis H, Eswar C, Gale J, Gannon MR, Jonnada S, Khaksar S, Lester JF, O'Sullivan JM, Parikh OA, Pedley ID, Pudney DM, Sheehan DJ, Srihari NN, Tran ATH, Parmar MKB, Sydes MR; Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet*. 2018 Dec 1;392(10162):2353-2366. doi: 10.1016/S0140-6736(18)32486-3. Epub 2018 Oct 21. PMID: 30355464; PMCID: PMC6269599.

9. **Parker CC, James ND, Brawley CD, Clarke NW, Ali A, Amos CL, Attard G, Chowdhury S, Cook A, Cross W, Dearnaley DP, Douis H, Gilbert DC, Gilson C, Gillessen S, Hoyle A, Jones RJ, Langley RE, Malik ZI, Mason MD, Matheson D, Millman R, Rauchenberger M, Rush H, Russell JM, Sweeney H, Bahl A, Birtle A, Capaldi L, Din O, Ford D, Gale J, Henry A, Hoskin P, Kagzi M, Lydon A, O'Sullivan JM, Paisey SA, Parikh O, Pudney D, Ramani V, Robson P, Srihari NN, Tanguay J, Parmar MKB, Sydes MR; STAMPEDE Trial Collaborative Group**. Radiotherapy to the prostate for men with metastatic prostate cancer in the UK and Switzerland: Long-term results from the STAMPEDE randomised controlled trial. *PLoS Med*. 2022 Jun 7;19(6):e1003998. doi: 10.1371/journal.pmed.1003998. PMID: 35671327; PMCID: PMC9173627.
10. **Reyes DK, Rowe SP, Schaeffer EM, Allaf ME, Ross AE, Pavlovich CP, Deville C, Tran PT, Pienta KJ**. Multidisciplinary total eradication therapy (TET) in men with newly diagnosed oligometastatic prostate cancer. *Med Oncol*. 2020 Jun 10;37(7):60. doi: 10.1007/s12032-020-01385-7. PMID: 32524295; PMCID: PMC7286864.