HHS Public Access

Author manuscript

J Clin Oncol. Author manuscript; available in PMC 2022 July 02.

Published in final edited form as:

J Clin Oncol. 2018 February 10; 36(5): 435–437. doi:10.1200/JCO.2017.76.5495.

STOMPing Out Hormone-Sensitive Metastases With Local Therapies in Prostate Cancer

Ryan M. Phillips,

Jonathan Hayman,

Phuoc T. Tran

Johns Hopkins Medicine, Baltimore, MD

With advances in detection and primary treatment, both with radical prostatectomy and definitive radiotherapy, the 92% of men diagnosed with prostate cancer in the local or regional stage can expect to live for decades with appropriate intervention.[1] The long disease-specific and overall survival observed with treated hormone-sensitive prostate cancer, particularly in the localized setting, are a result not only of primary treatment modalities, but also of the ever-evolving armamentarium of treatment approaches for men who recur, either locally or distantly, after definitive treatment. The management of locoregional recurrent prostate cancer comprises local salvage approaches including external-beam radiotherapy (EBRT), brachytherapy, prostatectomy, and cryotherapy, together with restaging to assess for nodal or distant metastases.

For patients with metastatic prostate cancer disease recurrence, the established approach is to offer androgen deprivation therapy (ADT), which improves survival but inevitably leads to castration resistance and can be associated with significant adverse effects.[2] The subsequent management of metastatic castrate-resistant prostate cancer is an exciting and rapidly advancing field dominated by systemic approaches including second-line ADT,

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

STOMPing Out Hormone-Sensitive Metastases With Local Therapies in Prostate Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Ryan M. Phillips
No relationship to disclose

Jonathan Hayman
No relationship to disclose

Phuoc T. Tran
Honoraria: Dendreon
Consulting or Advisory Role: Dendreon, Reflexion Medical
Research Funding: Astellas-Medivation
Patents, Royalties, Other Intellectual Property: Compounds and Methods of Use in Ablative Radiotherapy, patent No. 9114158

sipuleucel-T, taxanes, and radium-223.[3] However, although all these systemic options improve survival, they also remain noncurative modalities.

Debate continues about the very nature of metastatic progression, which classically has been considered a deterministic process wherein treatment failure in the localized setting leads to inevitable widespread progression. A compelling alternative is a spectrum-based model with localized and widely metastatic disease at its extremes with an intervening intermediate, low-volume, or oligometastatic state,[4] which is still amenable to definitive management through complete consolidation of all macroscopic tumor deposits.[5] Whether amenable to complete consolidation or not, metachronous or oligorecurrent prostate cancer affects a large number of men after failed primary therapy.[6–9]

The Surveillance or Metastasis-directed Therapy for Oligometastatic Prostate Cancer Recurrence (STOMP) trial described in the article that accompanies this editorial[10] sought to demonstrate whether the natural history of oligorecurrent prostate cancer could be altered with local therapies. STOMP is the first prospective, randomized, phase II trial to assess the potential of metastasis-directed therapies (MDT), primarily stereotactic ablative radiation (SABR), to forestall initiation of ADT in men with hormone-sensitive metastatic prostate cancer with three or fewer detectable metastases. This seminal and important prospective study directly validated in a rigorous fashion the observations of multiple retrospective studies showing a benefit of MDT in oligometastatic prostate cancer and mirrors recent progress in the field of oligometastatic lung cancer. Two recent randomized phase II trials in patients with non–small-cell lung cancer (NSCLC) with up to three to five metastases showed approximate tripling of progression-free survival with the addition of MDT to maintenance treatment compared with maintenance treatment alone,[11,12] possibly because of ablation of systemic therapy–resistant subpopulations that may have otherwise led to subsequent dissemination of treatment-refractory disease.[13] In line with this hypothesis, Gomez et al[11] demonstrated that local consolidation of macroscopic metastases delayed the time to development of new metastases.

As mentioned, several small retrospective studies in prostate cancer have reported on the safety and efficacy of MDT by SABR, focusing primarily on men with hormone-sensitive oligometastatic prostate cancer. Although eligibility, end points, and concurrent treatments varied somewhat among the studies, local control rates were > 95% at 14 months, with progression-free survival as high as 72% at 1 year and 54.5% at 3 years.[14–19] One report from Ghent University Hospital showed a median ADT-free survival interval of 38 months for men who received short neoadjuvant and concurrent ADT but in whom adjuvant ADT was deferred until evidence of progression.[14] Only two grade 3 adverse effects and no adverse effects of greater severity were observed among the 179 men reported in these various studies.

The primary outcome of the STOMP trial was ADT-free survival in men randomly assigned to surveillance alone versus MDT. The authors report median ADT-free survival of 21 versus 13 months for the MDT and surveillance arms, respectively. All patients for whom ADT was initiated purely because of local (n = 6) or symptomatic (n = 3) progression were from the surveillance arm, underlining the high efficacy of MDT for local control of individual

metastatic lesions. Nearly equal numbers of men in the MDT (n = 19) and surveillance (n = 16) arms received ADT because of polymetastatic progression, suggesting that there may have been distinct subpopulations within this oligorecurrent STOMP cohort, that is, those who had oligometastatic disease and where MDT influenced future macroscopic metastatic colonization versus those who had so-called oligovisible polymetastatic disease already beyond the practical reach of MDT alone. This concept will likely remain relevant to the study of oligometastatic disease because any definition that is based on quantifying detectable lesions will always be contingent on the sensitivity and specificity of the detection method used.[20] This is particularly germane given the rapid adoption of exquisitely sensitive prostate-specific membrane antigen positron emission tomography–computed tomography imaging worldwide.[21]

The authors also assessed MDT toxicity and found no grade 2 to 5 adverse events, which is consistent with the findings of prior retrospective studies. This reaffirms the safety of this approach, which is important when considering MDT as a way to forestall ADT or other systemic treatments associated with significant adverse effects. Along this same line of thinking, quality of life (QOL) was assessed at 3 months and 1 year. Differences in QOL at 3 months would signify benefit or harm related to early effects of MDT, but no difference was seen between groups, consistent with the low reported toxicity. Differential QOL outcomes at 1 year could reflect late effects of MDT, effects of ADT in men who progressed, or both, but no difference in QOL was appreciated at 1 year. Although we would expect ADT to influence certain response categories of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire PR25 (sexual activity, sexual function, and hormonal treatment-related symptoms), this study was not specifically powered to evaluate these differences.

As acknowledged in the article, the STOMP trial enrolled 62 patients and randomly assigned them 1:1 between arms, limiting the statistical power to detect differences in efficacy and lending itself to certain, perhaps inevitable, imbalances between those arms. For instance, the surveillance arm had more Gleason 6, low T-stage, and pN0 patients than did the MDTarm. Thus, the patients in the MDT arm indeed had more aggressive or more advanced disease at diagnosis, suggesting that the observed effect of MDT in STOMP may in fact be an underestimation.

To our knowledge, the STOMP trial is the first of such MDT trials for oligometastatic prostate cancer, and continued follow-up of the enrolled patient population will provide valuable details about the durability of this approach. However, additional complementary trials in this space will provide insight into the generalizability of these results. The Baltimore ORIOLE (ClinicalTrials.gov identifier: NCT02680587),[22] British CORE (ClinicalTrials.gov identifier: NCT02759783), Canadian PCS IX (ClinicalTrials.gov identifier: NCT02685397), French STEREO-OS (ClinicalTrials.gov identifier: NCT03143322), and OLIGOPELVIS (ClinicalTrials.gov identifier: NCT02274779/GETUG P07) trials are designed to evaluate the benefits of SABR as MDT for oligometastatic prostate cancer; CORE and STERO-OS are also enrolling patients with oligometastatic breast cancer or NSCLC.

Although the STOMP trial suggests that MDT is a promising approach to the multidisciplinary management of metastatic prostate cancer, this paradigm remains experimental. Twenty-one STOMP enrollees presented with nodal recurrence confined to the pelvis, including 13 in the MDTarm, five of whom received salvage pelvic lymph node dissection. Emerging evidence also suggests that appropriately selected patients may benefit from comprehensive pelvic nodal irradiation, with dose escalation to radiographically positive nodes. This approach entails greater upfront radiation exposure and the associated acute and long-term toxicities of pelvic radiation but may prophylactically treat tumor deposits too small to appreciate with current diagnostic detection limits. The roll of salvage pelvic lymph node dissection for recurrent prostate cancer within the pelvic lymph nodes as assessed by ^{68}Ga-prostate-specific membrane antigen positron emission tomography–computed tomography is being evaluated prospectively in a study sponsored by the Medical University of Vienna (ClinicalTrials.gov identifier: NCT02974075).

Forestalling systemic therapy is attractive to shield patients from adverse effects, but the combination of MDT and immediate ADT also warrants additional investigation. In patients not receiving MDT, immediate initiation of ADT can improve survival over delayed therapy,[23] and patients with low-volume disease appear to have improved overall survival with ADT and to gain more benefit from ADT than do those with greater disease burden. To date, an overall survival benefit from single-modality chemotherapy as management for oligometastatic prostate cancer has not been appreciated in large studies, but such a benefit may exist in patients prone to castration resistance.[24] The combination of hormonal agents, chemotherapy, or radiopharmaceutical agents such as radium-223 with MDT is an active area of study and in the future will be clinically relevant for the treatment of patients with higher-risk oligorecurrent prostate cancer.

Whether microscopic deposits are capable of persisting in the context of total consolidation of macroscopic tumor burden remains an unanswered question that will only be answered through continued exploration of the biologic underpinnings of prostate cancer metastasis and response to local and systemic therapies. Preclinical data suggest a unique biology of oligometastases in NSCLC regulated by microRNA-mediated attenuation of prometastatic epithelial plasticity programs such as the epithelial-mesenchymal transition.[25] We and others have shown that similar epithelial plasticity programs are sufficient and seem to be important clinically for prostate cancer metastasis.[26,27] Thus, it is critical that we understand the genomic, transcriptional, and signaling differences that may exist between tumors capable of widespread dissemination compared with those that appear to be restricted to a few favorable niches and, by extension, whether all low-volume disease is destined to disseminate widely.[28,29] In addition, the interactions between tumors and their local microenvironment, additional spatially distinct metastases, and the immune system also bear continued investigation.[30] The Movember Global Action Plan 6 initiative on oligometastatic prostate cancer will be directly investigating many of these critical biologic and clinical questions.[31]

Great progress has been made in the management of prostate cancer, but important questions remain, particularly regarding the management of oligometastatic disease. The STOMP trial

represents an important advance in this pursuit and provides a strong argument for continued investigation of the role of MDT in the management of oligometastatic prostate cancer.

Acknowledgment

Supported by the Nesbitt-McMaster Foundation (P.T.T.), Grant LCD-339465 from the American Lung Association, Movember, the Prostate Cancer Foundation, and Grants No. R01CA166348 and U01CA183031 from the National Institutes of Health.

REFERENCES

1. American Cancer Society: Cancer Facts & Figures 2017. Atlanta, GA, American Cancer Society, 2017.
2. Nguyen PL, Alibhai SM, Basaria S, et al. : Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur Urol 67:825–836, 2015 [PubMed: 25097095]
3. Virgo KS, Basch E, Loblaw DA, et al. : Second-line hormonal therapy for men with chemotherapy-naïve, castration-resistant prostate cancer: American Society of Clinical Oncology provisional clinical opinion. J Clin Oncol 35:1952–1964, 2017 [PubMed: 28441112]
4. Hellman S, Weichselbaum RR: Oligometastases. J Clin Oncol 13:8–10, 1995 [PubMed: 7799047]
5. Tran PT, Antonarakis ES: Altering the natural history of oligometastatic prostate cancer with local therapies: Reality versus illusion. J Oncol Pract 13:21–24, 2017 [PubMed: 28045614]
6. Soloway MS, Hardeman SW, Hickey D, et al. : Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. Cancer 61:195–202, 1988 [PubMed: 3334948]
7. Singh D, Yi WS, Brasacchio RA, et al. : Is there a favorable subset of patients with prostate cancer who develop oligometastases? Int J Radiat Oncol Biol Phys 58:3–10, 2004 [PubMed: 14697414]
8. Schweizer MT, Zhou XC, Wang H, et al. : Metastasis-free survival is associated with overall survival in men with PSA-recurrent prostate cancer treated with deferred androgen deprivation therapy. Ann Oncol 24:2881–2886, 2013 [PubMed: 23946329]
9. Sridharan S, Steigler A, Spry NA, et al. : Oligometastatic bone disease in prostate cancer patients treated on the TROG 03.04 RADAR trial. Radiother Oncol 121:98–102, 2016 [PubMed: 27528117]
10. Ost P, Reynders D, Decaestecker K, et al. : Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: A prospective, randomized, multicenter phase II trial. J Clin Oncol 36:446–453, 2018 [PubMed: 29240541]
11. Gomez DR, Blumenschein GR Jr, Lee JJ, et al. : Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: A multicentre, randomised, controlled, phase 2 study. Lancet Oncol 17:1672–1682, 2016 [PubMed: 27789196]
12. Iyengar P, Wardak Z, Gerber DE, et al. : Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: A phase 2 randomized clinical trial. JAMA Oncol [epub ahead of print on September 24, 2017] 10.1001/jamaoncol.2017.3501
13. Hong MK, Macintyre G, Wedge DC, et al. : Tracking the origins and drivers of subclonal metastatic expansion in prostate cancer. Nat Commun 6:6605, 2015 [PubMed: 25827447]
14. Berkovic P, De Meerleer G, Delrue L, et al. : Salvage stereotactic body radiotherapy for patients with limited prostate cancer metastases: Deferring androgen deprivation therapy. Clin Genitourin Cancer 11:27–32, 2013 [PubMed: 23010414]
15. Decaestecker K, De Meerleer G, Lambert B, et al. : Repeated stereotactic body radiotherapy for oligometastatic prostate cancer recurrence. Radiat Oncol 9:135, 2014 [PubMed: 24920079]
16. Jereczek-Fossa BA, Beltramo G, Fariselli L, et al. : Robotic image-guided stereotactic radiotherapy, for isolated recurrent primary, lymph node or metastatic prostate cancer. Int J Radiat Oncol Biol Phys 82:889–897, 2012 [PubMed: 21277113]
17. Muacevic A, Kufeld M, Rist C, et al. : Safety and feasibility of image-guided robotic radiosurgery for patients with limited bone metastases of prostate cancer. Urol Oncol 31:455–460, 2013 [PubMed: 21481619]

18. Schick U, Jorcano S, Nouet P, et al. : Androgen deprivation and high-dose radiotherapy for oligometastatic prostate cancer patients with less than five regional and/or distant metastases. Acta Oncol 52:1622–1628, 2013 [PubMed: 23544357]
19. Tabata K, Niibe Y, Satoh T, et al. : Radiotherapy for oligometastases and oligo-recurrence of bone in prostate cancer. Pulm Med 2012:541656, 2012 [PubMed: 22991663]
20. Tosoian JJ, Gorin MA, Ross AE, et al. : Oligometastatic prostate cancer: Definitions, clinical outcomes, and treatment considerations. Nat Rev Urol 14: 15–25, 2017 [PubMed: 27725639]
21. Murphy DG, Sweeney CJ, Tombal B: "Gotta catch 'em all", or Do we? Pokemet approach to metastatic prostate cancer. Eur Urol 72:1–3, 2017 [PubMed: 28283344]
22. Radwan N, Phillips R, Ross A, et al. : A phase II randomized trial of Observation versus stereotactic ablative RadiatIon for OLigometastatic prostate CancEr (ORIOLE). BMC Cancer 17:453, 2017 [PubMed: 28662647]
23. Duchesne GM, Woo HH, Bassett JK, et al. : Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01–03 [TOAD]): A randomised, multicentre, non-blinded, phase 3 trial. Lancet Oncol 17:727–737, 2016 [PubMed: 27155740]
24. Dorff TB, Sweeney CJ: Chemotherapy for oligometastatic prostate cancer. Curr Opin Urol 27:553–558, 2017 [PubMed: 28817399]
25. Uppal A, Wightman SC, Mallon S, et al. : 14q32-encoded microRNAs mediate an oligometastatic phenotype. Oncotarget 6:3540–3552, 2015 [PubMed: 25686838]
26. Malek R, Gajula RP, Williams RD, et al. : TWIST1-WDR5-hottip regulates Hoxa9 chromatin to facilitate prostate cancer metastasis. Cancer Res 77: 3181–3193, 2017 [PubMed: 28484075]
27. Lo UG, Lee CF, Lee MS, et al. : The role and mechanism of epithelial-to-mesenchymal transition in prostate cancer progression. Int J Mol Sci 18:2079, 2017
28. Boutros PC, Fraser M, Harding NJ, et al. : Spatial genomic heterogeneity within localized, multifocal prostate cancer. Nat Genet 47:736–745, 2015 [PubMed: 26005866]
29. Robinson D, Van Allen EM, Wu YM, et al. : Integrative clinical genomics of advanced prostate cancer. Cell 161:1215–1228, 2015 [Erratum: Cell 162:454, 2015] [PubMed: 26000489]
30. Gundem G, Van Loo P, Kremeyer B, et al. : The evolutionary history of lethal metastatic prostate cancer. Nature 520:353–357, 2015 [PubMed: 25830880]
31. Movember Foundation: GAP6 - oligometastatic prostate cancer. https://gap6.fluidreview.com/