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External beam radiation therapy carries lower risk of sexual dysfunction as compared to radical prostatectomy in treatment of patients with localized prostate cancer

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ABSTRACT A clinical decision report appraising:

Donovan JL, Hamdy FC, Lane JA, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *N Engl J Med*. 2016;375(15):1425-1437. https://doi.org/10.1056/NEJMoa1606221

for a patient with localized prostate cancer and concerns regarding future sexual dysfunction.

Keywords: *radical prostatectomy, prostate cancer, external beam radiation therapy, erectile dysfunction*

Clinical-Social Context

Gordon Freeman (pseudonym), a 69 year old upper-middle class white man with no significant past medical history presented to his urologist with a routine screening prostate-specific antigen (PSA) of 4.20. He reported no associated symptoms although his family history was significant for prostate cancer in his brother diagnosed at age 73 and treated with radical prostatectomy. Digital rectal exam (DRE) revealed an age-appropriate, slightly enlarged prostate gland with no nodularity. A 12-core transrectal ultrasound-guided prostate biopsy confirmed the diagnosis of prostate cancer with 4 cores of Gleason 3+3=6 disease along with a single core of Gleason 3+4=7 disease. Taken together with his PSA and DRE findings, Mr. Freeman's prostate cancer was classified as T1c and favorable intermediate risk.[1] Per National Comprehensive Cancer Network (NCCN) guidelines,[1] Mr. Freeman was offered three options: active surveillance, definitive surgical treatment by radical prostatectomy, or definitive radiation treatment by external beam radiation therapy (EBRT). As Mr. Freeman's wife had recently passed after a lengthy battle with breast cancer, Mr. Freeman elected for definitive therapy over surveillance. In choosing between the comparably efficacious[2] treatment modalities of surgery and radiation, Mr. Freeman's primary concern was preservation of his sexual and urinary function as he lived alone in an apartment with no family nearby to help. Although his brother had elected for surgical management, Mr. Freeman was hesitant to undergo surgery as his brother experienced ongoing erectile dysfunction after his prostatectomy.

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Clinical Question

Does definitive external beam radiation therapy for men with prostate cancer offer significantly greater preservation of sexual function than radical prostatectomy?

Research Article

Donovan JL, Hamdy FC, Lane JA, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *The New England Journal of Medicine*, 2016;375(15):1425-1437. https://doi.org/10.1056/NEJMoa1606221.[6]

Description of Related Literature

The literature review began by searching PubMed with the search query “radical prostatectomy” AND “radiation therapy” AND “prostate cancer” AND “quality of life” sorted by best match. This search yielded 569 total results, including 43 clinical trials, 161 review articles, and 12 meta-analyses.

To narrow down these results, an UpToDate search using the search query “prostate cancer initial management” was performed. The top result from this search, an article titled “Prostate cancer: Risk stratification and choice of initial treatment”, discussed quality of life issues after initial treatment of prostate cancer by external beam radiation therapy (EBRT) versus radical prostatectomy and cited four prospective studies,[3-6] each of which also appeared in the top 10 results from the PubMed search. Thus, these articles were most heavily considered for appraisal.

The Sanda et al. trial[3] was a multicenter trial including 1201 patients with previously untreated stage T1 to T2 prostate cancer. The Barocas et al. trial[4] was a prospective observational trial with a broad cohort of 2550 patients from five Surveillance, Epidemiology, and End Results (SEER) registries from New Jersey to California with stage T1 to T2 localized prostate cancer enrolled within 6 months of diagnosis. Finally, the Chen et al. trial[5] enrolled 1141 men with newly diagnosed prostate cancer from the North Carolina Central Cancer Registry. Each of these trials compared quality of life outcomes including sexual function among patients receiving active surveillance, EBRT, or radical prostatectomy. However, each of these trials was an observational trial wherein patients who independently chose surgery versus radiation were prospectively followed. This lack of randomization meant that patients choosing EBRT were more likely to have significant comorbidities which made them poor surgical candidates, and which could potentially predispose them to more negative outcomes. Therefore, the Sanda et al., Barocas et al., and Chen et al. trials were deemed poor matches for Mr. Freeman, who had no significant comorbidities at diagnosis and was an excellent candidate for surgery as well as EBRT.

The last trial, however, was a prospective phase III randomized, controlled trial. The ProtecT study[6] (Prostate Testing for Cancer and Treatment) enrolled 1643 patients who received a diagnosis of prostate cancer and were randomized to active surveillance, radical prostatectomy, or EBRT. Although the primary endpoint was disease-specific mortality, patient-reported quality of life outcomes were included as a secondary endpoint. Like the other studies, this study also directly addressed the clinical question. However, unlike the other studies, the randomization in this study ensured that the EBRT arm did not include poor surgical candidates by default. Therefore, this study best matched Mr. Freeman, who had no significant past medical history or comorbidities.

After locating the chosen article in Google Scholar and filtering for “Related Articles,” one other study was identified, but it was observational and had similar outcomes to the article chosen for critical appraisal.[7]

Using SORT criteria, the literature guiding treatment for prostate cancer with an emphasis on sexual and urinary function is Strength of Recommendation B, based on limited, medium quality clinical trials.[8]

Critical Appraisal

From 1999-2009, the ProtecT trial recruited 228,966 men aged 50-69 years and registered at 337 primary care centers across nine cities in the United Kingdom. Of this group, 82,429 men agreed to a PSA test in that time period with 8566 patients having a PSA in the study inclusion range between 3.0 and 20.0. Of these men, 2664 received a biopsy-proven diagnosis of prostate cancer. Finally,

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1643 of those patients agreed to randomization in a 1:1:1 ratio with 545 men each assigned to active surveillance or EBRT and 553 assigned to open retropubic nerve sparing radical prostatectomy. Exclusion criteria included previous non-skin cancer, previous renal transplant, current renal dialysis, major cardiorespiratory comorbidities, bilateral hip replacement, or life expectancy less than 10 years. Patient characteristics, including demographics, PSA at diagnosis, Gleason score, and T stage, were all evenly distributed among the three trial arms as demonstrated by matching percentage distributions.

The study results demonstrated that the each of the three treatment arms had 98.8% or greater, 10-year prostate cancer-specific survival rates as the primary endpoint. The differences among the three arms were insignificant ($p = 0.48$). The outcomes of sexual function were assessed by expanded prostate cancer index composite (EPIC) questionnaire. While all three groups had comparable (65.7% - 68.4%, no p-value provided) erection firmness (sufficient for sexual intercourse) score at baseline, the EBRT (27.4%) and active surveillance (29.6%) groups had comparable (no p-value provided) erectile function at 72-month follow up, which was significantly greater than that in the radical prostatectomy group (16.5%, $p < 0.001$). At the 72-month time point, the number needed to treat with EBRT over radical prostatectomy to prevent one case of erectile dysfunction was 9.1.

Notable weaknesses of the study include limited inclusion of modern robotic prostatectomy, which constituted only 25 of the 553 prostatectomies (versus 324 open procedures). While observational studies have shown that robotic prostatectomy has comparable sexual function outcomes at 12 months as compared to open procedure, additional follow up is required to determine long-term outcomes. Moreover, all patients in the EBRT arm received 3-6 month neoadjuvant and concurrent androgen deprivation therapy (ADT), which has an established side-effect of erectile dysfunction.[7] Per NCCN guidelines,[1] ADT is not indicated for Mr. Freeman's favorable intermediate risk prostate cancer. However, the long-term outcomes at 72-months were comparable between EBRT and active surveillance in spite of the temporary ADT in the EBRT arm. Therefore, EBRT without ADT would likely feature comparable long-term outcomes with relatively improved sexual function at the 6-month time point where EBRT (with ADT) demonstrated 22% erectile function versus 12% in the radical prostatectomy group ($p < 0.001$) and 52% in the active surveillance group ($p < 0.001$). According to the SORT criteria,[8] this conclusion is consistent with Level 1 quality as the ProtecT trial is a high quality randomized, controlled trial that follows the results out to the long-term 72-month mark and focuses on a very patient-oriented outcome. Moreover, the conclusion is consistent with that of the previously mentioned studies.[3-5]

Naturally, this study could not be blinded or placebo-controlled as no sham surgeries (with associated anesthesia risks) could ethically be considered. Unlike the other considered observational studies, this study featured patients who were prospectively randomized, and each trial arm had comparable clinical and demographic characteristics, so there was minimal selection bias. Of the 2664 patients with diagnosed prostate cancer, 1643 (61%) agreed to randomization into the three trial arms. While the 61% response rate of invited patients may introduce participation bias, this value was actually slightly larger than that of the other considered articles.[3-5] Therefore, this study would likely have the least participation bias of the group.

The analyses carried out within each trial arm were completed on an intention-to-treat basis, increasing the strength of the trial to guide patient care decisions. Attrition bias was minimal as only 14 patients (1%) dropped out of the study. The study was registered prospectively without deviation from the treatment protocol and the funding was publicly provided by the UK National Institute for Health Research. While the study population was 98% white, this was representative of the facilities from which participants were recruited.

Clinical Application

This study concluded that all forms of NCCN-guided management of favorable intermediate risk prostate cancer (radical prostatectomy, EBRT, or active surveillance) were very highly and comparably efficacious in preventing prostate cancer-specific mortality. However, sexual function was significantly diminished in the radical prostatectomy group as compared to either the active surveillance or EBRT groups.

The clinical and demographic background of the patients in this study closely match that of the patient presented in the clinical-social context. Like Mr. Freeman, the study population was predominantly white and excluded those with significant comorbidities. Therefore, the authors' conclusions should apply to Mr. Freeman as well.

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Based on the appraisal of the ProtecT trial, either active surveillance or EBRT would be appropriate for Mr. Freeman to best preserve his sexual function in the long term while not sacrificing therapeutic efficacy. After discussion of these options with Mr. Freeman, he elected to undergo definitive treatment by EBRT. He is currently undergoing EBRT treatments at our facility and his PSA will be followed. If the PSA reaches a nadir after treatment, then he will be followed per NCCN guidelines by PSA screening every 6 months.[1]

New Knowledge Related to Clinical Decision Science

Clinical Decision Science requires a holistic perspective on the practice of medicine. This entire clinical decision report is based on Mr. Freeman presenting with "a routine screening prostate-specific antigen (PSA) of 4.20". For a 69 year old man who just lost his spouse to cancer, is getting a "routine screening PSA" appropriate? The fact that he has a lower grade prostate cancer only emphasizes the importance of that question. How close was Mr. Freeman to his 70th birthday when screening is no longer recommended? Understanding "age" is arbitrary when issuing guidelines, clinical decision science would probably have highlighted the importance of asking Mr. Freeman," How do you plan to celebrate your 70th birthday now that your wife is no longer here?" BEFORE ordering a screening PSA. Perhaps exploring this patient's social context is as important as any of the other clinical decisions that were made in this whole episode of care. Without family nearby, Mr. Freeman is already coping with multiple life changes. With his concern about preserving erectile functioning, perhaps Mr. Freeman has concerns about future intimate relationships. When these issues are addressed is important.

Another fallacy is that Mr. Freeman must choose between the three options that correlate with the randomization groups in the clinical research evidence. Knowing that there is no difference in long term survival, a decision-making process could honor Mr. Freeman's desire for definitive treatment in a phased approach. Being in a state of active bereavement of his wife from a cancer-related disease, dealing with the issues of grief before rushing to decisions related to cancer treatment seem to be of paramount importance. Perhaps Mr. Freeman would have different perspectives after three or four months have passed.

Additionally, just because Mr. Freeman has "no family nearby" to help with doctor appointments or other healthcare related tasks doesn't mean that physicians shouldn't offer telehealth options to "gather" his family to support him in this decision-making process. Mr. Freeman's response to such an offer does give the practitioner a sense of family support for the inevitable future health challenges that Mr. Freeman will face.

Conflict Of Interest Statement

The author declares no conflicts of interest.

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