



## EDITORIAL

# Long-term patient follow-up should be routinely implemented in radiotherapy units to detect late adverse effects after cancer treatment

Editorial comment to Urosymphyseal fistula after pelvic radiotherapy – an entity in patients with significant comorbidity requiring multidisciplinary management *Scand J Urol.* 2023

Kirsti Aas<sup>a</sup> and Amir Sherif<sup>b,c</sup>

<sup>a</sup>Consultant Urological Surgeon and Associate Professor, Akershus University Hospital, Norway; Faculty of Medicine, University of Oslo, Norway; <sup>b</sup>Consultant Urological Surgeon and Associate Professor, Norrlands University Hospital, Sweden; <sup>c</sup>Department of Surgical and Perioperative Sciences, University of Umeå, Sweden

### ARTICLE HISTORY

Accepted 21 June 2023

It is well known that curatively intended cancer treatment may result in short- and long-term adverse effects with a negative impact on patients' quality of life. That sequelae after such treatment may result in need of major surgery and death is less recognized.

In the current issue of the *Scandinavian Journal of Urology*, Brändstedt et al. present a cohort of patients with urosymphyseal fistulas (USFs) after pelvic radiotherapy in a tertiary referral center in Sweden. The authors bring to attention a complex condition requiring multidisciplinary management (urological, orthopaedic, colorectal, infectious disease) and extensive surgical interventions in the majority of cases. Within few years of diagnosis, one in three men had died as a direct consequence of USF.

Radiotherapy is administered in highly specialized centers, and long-term patient follow-up is mainly organized within the primary health care services. Adverse effects related to the urinary tract (e.g. USFs, secondary bladder cancers, radiation cystitis, urethral or ureteral strictures, bladder contractures and dysfunction) may manifest long after pelvic radiotherapy and are generally managed within local or regional urology departments [1–9]. Unless long-term patient follow-up is routinely implemented by the cancer therapy units, late complications escape the attention of the radiation physicians. Local radiation toxicity often becomes evident during the first years after treatment, but the cumulative incidence of adverse post-radiotherapy events continues to increase with time [10, 11]. In the current literature, there is a paucity of population-based data on late complications and mortality after pelvic radiotherapy.

In our clinical experience, urology departments are frequently visited by patients with post-radiotherapy complications involving the urinary tract. Direct and indirect sequelae after

pelvic radiotherapy may lack specific diagnostic codes (like USFs) and conditions may not be coded with the external cause of morbidity that is radiotherapy. Therefore, complete adverse event data cannot be easily retrieved retrospectively from electronic journals or public health registries. For USF after pelvic radiotherapy, only case reports and small case series are described in the literature. The case series from Skåne University Hospital is a prudent attempt to present population-data on USF, however, when post-treatment outcome data have not been prospectively collected, the real-world prevalence still remains unknown. Late adverse effect profiles of new radiation regimens cannot be compared with older methods when historical data are missing [12, 13].

The majority of the patients in the Skåne cohort were elderly with significant comorbidities and had undergone primary or salvage radiotherapy for prostate cancer median 5 years prior to the diagnosis of USF. It would be interesting to know the patient characteristics at the time of curatively intended radiotherapy, being aware that these men suffered severe treatment-related morbidity, and in some cases death, few years later. This could help in identification of specific groups with increased risk of USF. The potential late and severe side-effects following radiotherapy must be recognized by physicians and properly communicated to patients at increased risk so they can make informed decisions about their treatment, particularly when other options are available. Patients who are deemed unfit for or have previously undergone surgery, however, are often referred for radiotherapy as the only remaining curative treatment alternative. As with surgery, higher age and comorbidity increase the risk of adverse effects after radiotherapy [14, 15].

The authors importantly highlight an increased risk of secondary complications for patients who are managed with

invasive procedures for local sequelae of the urinary tract after radiotherapy. The cause–effect relationship of urological interventions and USFs in previously irradiated patients, however, cannot be concluded based on the current material. The findings implicate that patients with urinary complications after radiotherapy may benefit from management in more experienced centers, to avoid secondary unwanted effects of invasive investigations and treatments.

For patients with USFs, it is correctly emphasized that a multidisciplinary approach is likely to improve diagnostic workup and treatment. An early raised suspicion of USF should lead to referral to a highly specialized hospital in order to avoid suboptimal management in smaller centers lacking the experience of such entities. The early use of MRI seems reasonable and attainable in local centers. The authors present a wide range of therapeutic approaches, including extensive surgery as the only definitive treatment, in a widely heterogenic group of patients. It is clear that multidisciplinary treatment approaches need to be tailored individually. The lack of guidelines on USF management support the need to centralize care to obtain sufficient experience. This would also be beneficial in terms of population-based registration and research into this presumably rare condition.

With their study, Brändstedt et al. have successfully increased the awareness and knowledge about USFs after pelvic radiotherapy. In our opinion, long-term patient follow-up should be routinely implemented in radiotherapy units to document late adverse effects after cancer treatment, ultimately improving patient selection and counselling.

## References

- [1] Moschini M, Zaffuto E, Karakiewicz PI, et al. External beam radiotherapy increases the risk of bladder cancer when compared with radical prostatectomy in patients affected by prostate cancer: A population-based analysis. *Eur Urol.* 2019;75(2):319–28. <https://doi.org/10.1016/j.eururo.2018.09.034>
- [2] Guo X, Liu M, Hou H, et al. Impact of prostate cancer radiotherapy on the biological behavior and specific mortality of subsequent bladder cancer. *Int J Clin Oncol.* 2019;24(8):957–65. <https://doi.org/10.1007/s10147-019-01427-9>
- [3] Zhao S, Xie Q, Yang R, et al. High prevalence of secondary bladder cancer in men on radiotherapy for prostate cancer: evidence from a meta-analysis. *Cancer Manag Res.* 2019;11:587–98. <https://doi.org/10.2147/CMAR.S185867>
- [4] Martin SE, Begun EM, Samir E, Azaiza MT, Allegro S, Abdelhady M. Incidence and morbidity of radiation-induced hemorrhagic cystitis in prostate cancer. *Urology.* 2019;131:190–5. <https://doi.org/10.1016/j.urology.2019.05.034>
- [5] Makino K, Sato Y, Takenaka R, et al. Cumulative incidence and clinical risk factors of radiation cystitis after radiotherapy for prostate cancer. *Urol Int.* 2023;107(5):440–447. <https://doi.org/10.1159/000521723>
- [6] Carlsson S, Bock D, Lantz A, et al. Salvage radiotherapy after radical prostatectomy: functional outcomes in the LAPPRO trial after 8-year follow-up. *Scand J Urol.* 2023;58:11–9. <https://doi.org/10.2340/sju.v58.7318>
- [7] Braide K, Kindblom J, Thellenberg Karlsson C, Stattin P, Hugosson J, Mansson M. Risk of severe late toxicity after radiotherapy following radical prostatectomy – a nationwide study. *BJU Int.* 2022;130(6):799–808. <https://doi.org/10.1111/bju.15769>
- [8] Fridriksson JO, Folkvaljon Y, Nilsson P, et al. Long-term adverse effects after curative radiotherapy and radical prostatectomy: population-based nationwide register study. *Scand J Urol.* 2016;50(5):338–45. <https://doi.org/10.1080/21681805.2016.1194460>
- [9] David RV, Kahokehr AA, Lee J, Watson DI, Leung J, O’Callaghan ME. Incidence of genitourinary complications following radiation therapy for localised prostate cancer. *World J Urol.* 2022;40(10):2411–22. <https://doi.org/10.1007/s00345-022-04124-x>
- [10] Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol.* 2016;17(8):1047–60. [https://doi.org/10.1016/S1470-2045\(16\)30102-4](https://doi.org/10.1016/S1470-2045(16)30102-4)
- [11] Lane JA, Donovan JL, Young GJ, et al. Functional and quality of life outcomes of localised prostate cancer treatments (Prostate Testing for Cancer and Treatment [ ProtecT ] study). *BJU Int.* 2022;130(3):370–80. <https://doi.org/10.1111/bju.15739>
- [12] Yu T, Zhang Q, Zheng T, et al. The effectiveness of intensity modulated radiation therapy versus three-dimensional radiation therapy in prostate cancer: a meta-analysis of the literatures. *PLoS One.* 2016;11(5):e0154499. <https://doi.org/10.1371/journal.pone.0154499>
- [13] Kerkmeijer LGW, Groen VH, Pos FJ, et al. Focal boost to the intraprostatic tumor in external beam radiotherapy for patients with localised prostate cancer: results from the FLAME randomized phase III trial. *J Clin Oncol.* 2021;39(7):787–96. <https://doi.org/10.1200/JCO.20.02873>
- [14] Hamstra DA, Stenmark MH, Ritter T, et al. Age and comorbid illness are associated with late rectal toxicity following dose-escalated radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2013;85(5):1246–53. <https://doi.org/10.1016/j.ijrobp.2012.10.042>
- [15] David R, Hiwase M, Kahokehr AA, et al. Predicting post-radiation genitourinary hospital admissions in patients with localised prostate cancer. *World J Urol.* 2022;40(12):2911–8. <https://doi.org/10.1007/s00345-022-04212-y>