Radical radiotherapy for prostate cancer: patterns of care in Sweden 1998–2016

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ABSTRACT

Introduction: Radiotherapy is an established treatment option for prostate cancer (PCa), both as primary treatment and secondary treatment after radical prostatectomy (RP). Since 1998, detailed data on radiotherapy delivered to Swedish men with PCa (e.g. treatment modalities, absorbed doses, fractionation) have been collated within PCa data Base Sweden (PCBaSe). This study reports patterns of radical radiotherapy for PCa in Sweden over the past two decades.

Materials and methods: All men with non-metastatic PCa (1998–2016) who received external beam radiotherapy (EBRT) or high or low dose-rate brachytherapy (HDR-BT/LDR-BT) were identified in PCBaSe. Analyses included: trends in radiation techniques, fractionation patterns and total doses over time; PCa-specific survival comparing treatment in 2007–2017 with 1998–2006; and regional variation in type of primary radiotherapy.

Results: About 20,876 men underwent primary radiotherapy. The main treatment modalities include conventionally fractionated (2.0 Gy/fraction) EBRT (51%), EBRT with HDR-BT boost (27%) and hypofractionated (>2.4 Gy/fraction) EBRT (11%). EBRT with photon or proton boost and HDR-BT and LDR-BT monotherapies were each used minimally. Use of dose-escalated EBRT (>74 Gy) and moderate hypofractionation increased over time, while use of HDR-BT declined. Considerable regional variation in treatment modalities was apparent. Risk of PCa death following primary radiotherapy had declined for intermediate-risk (HR: 0.60; 95%CI 0.47–0.87) and high-risk PCa (HR: 0.72; 95%CI 0.61–0.86).

Discussion: Increased use of dose escalation and hypofractionated EBRT has occurred in Sweden over the past two decades, reflecting current evidence and practice guidelines. Disease-specific outcomes have also improved. Data collected in PCBaSe provide an excellent resource for further research into RT use in PCa management.

Introduction

Radical radiotherapy is a primary treatment option for prostate cancer (PCa), and also a common treatment strategy for biochemical recurrence after radical prostatectomy (RP). Different radical radiotherapy options include external beam radiotherapy (EBRT), high-dose rate brachytherapy (HDR-BT) combined with EBRT, and low-dose rate brachytherapy (LDR-BT) or HDR-BT used as monotherapies [1–3]. Substantial changes in techniques, delivery methods, and radiotherapy absorbed doses and fractionation schemes for PCa have occurred over the past two decades [4]. Thus, assessment of clinical outcomes, adverse effects or quality of life following radiotherapy for PCa is difficult without detailed data on treatment modalities, given doses and radiotherapy delivery modes.

Given the variety of treatments, there is a need to assess the effectiveness of different types of radiation treatments for PCa to inform best practice. In addition, there is an interest in assessing the superiority of dose escalated (e.g. total dose >74–80 Gy) [5,6], moderately hypofractionated EBRT (>2.4–3.4 Gy per fraction) [7,8], and ultra-hypofractionated EBRT (>5 Gy per fraction) [9] over conventional dose EBRT (e.g. total dose of 68–74 Gy), as well as determining the fractionation sensitivity of PCa [10]. Randomised clinical trials (RCT) are the gold standard for comparison between different treatments. However, the assessment of outcomes of these treatments in clinical practice, where the indication for treatment is broader and patients are often frailer or have more advanced disease, is also needed since results obtained in RCTs may not be achievable in this setting [11]. Furthermore, information on types of radiotherapy received by men with PCa can provide insights into whether current practice aligns with evidence or clinical guidelines. Hence, there is a need for data on the use of radiation therapies for
PCa and outcomes of these treatments from large representative cohorts.

This article describes the collection of radiotherapy data in a nationwide, population-based cohort of Swedish men with PCa. We present trends in radiotherapy treatments over two decades, describe regional variations in use of radiotherapy and compare disease-specific survival over two time periods. This study presents descriptive analysis and does not formally test any hypotheses. Rather, its aims are to generate hypotheses and stimulate further research that could be undertaken using this data resource.

Materials and methods

Data sources

The National Prostate Cancer Register [NPCR] collects detailed information on clinical characteristics, work-up and primary treatments for men diagnosed with PCa in Sweden since 1998 [12]. NPCR includes data on 98% men diagnosed with PCa compared with the Swedish Cancer Register, to which reporting is mandatory [13]. Data quality in the NPCR is high [14]. Using Swedish residents’ unique personal identification number, NPCR has been linked with other national registries including the National Patient Register [NPR], National Prescribing Drug Register [NPDR], Longitudinal Integration Database for Insurance and Labour Market Studies [LISA], Multi-Generation Register and the Cause of Death Register to create Prostate Cancer data Base Sweden [PCBaSe] [15,16]. An overview of the data collection and linkage processes that make up the current version of PCBaSe (Version 4.1) are shown in Figure 1.

Information on primary treatment (or intended treatment if primary treatment had not commenced within 6 months of diagnosis) has been collected in NPCR since 1998 for all newly diagnosed men. Since 2008, radiotherapy specific data have been collected from oncology departments providing radiation therapy, via a separate form, for all men who received primary or secondary radical radiotherapy. Data items include start and stop dates, treatment modality, dose per fraction, total dose, use of implanted markers for EBRT image guidance, and target (inclusion of seminal vesicles and/or regional lymph nodes) of radiotherapy, neoadjuvant and adjuvant androgen deprivation therapy (ADT).

The most recent version of the radiotherapy form is provided in the Supplementary Figure S1. A retrospective data audit (known as RetroRAD) collected data directly from the Oncology Information Systems and local databases at 17 of the 18 radiotherapy centres in Sweden on primary and secondary radical radiotherapy from 1998 to 2008 for inclusion in PCBaSe. RetroRAD does not contain information on any extra-prostatic targets. In 2015, data collection in NPCR was extended to include more details on RP procedures, histopathological examination of the surgical specimen

Figure 1. PCBaSe 4.1 data collection and linkages.
(pathological stage, Gleason score and margin status) and clinical characteristics prior to secondary radiotherapy after prostatectomy [17]. Between 2008 and 2015, prior to the addition of the prostatectomy form, capture of secondary radiotherapy was not complete and data are limited for pre-radiotherapy clinical characteristics.

To assess the use of ADT in conjunction with primary RT, dates of prescriptions for anti-androgens (AA) and gonadotrophin releasing hormone agonists (GnRH) were extracted from the NPDR using linkage via individual personal identification numbers. Neoadjuvant ADT was defined as at least one filled prescription within a 90-day period before their RT start date, while adjuvant RT was defined as at least one prescription from RT start date to 180 days after RT start. These data were only available from 2006 onward.

**Statistical analysis**

A consort flow diagram showing the selection of study participants for analysis of primary radiotherapy is presented in Supplementary Figure S2. All men with non-metastatic PCa diagnosed between 1998 and 2016, who had radiotherapy recorded as their primary treatment were identified in NPCR. Primary radiotherapy was defined as the receipt of radical radiation therapy to the prostate within 2 years of diagnosis, with or without neoadjuvant or adjuvant ADT, and no prior indication of RP or period of active surveillance (AS). Conventionally fractionated EBRT with total doses below 60 Gy and no additional boost was considered palliative therapy and such cases were excluded. Men who had undergone prostatectomy prior to radiotherapy, or received pelvic lymph node dissection (PLND) only, were identified through the linkage with the NPR and excluded. (Before 2005, PLND prior to radiotherapy as a diagnostic procedure to rule out lymph node metastases was common.) Men with missing data on radiotherapy start date, modality or dose were excluded from the analytic cohort.

For descriptive analyses, primary radiotherapy was classified into seven categories: conventionally fractionated (2.0 Gy per fraction) EBRT with total doses ranging from 60 to 82 Gy; moderately or ultra-hypofractionated EBRT with doses per fraction ranging from 2.4 to 6 Gy; conventionally fractionated EBRT with photon boost (typically $25 \times 2.0 \text{ Gy} + 4 \times 5.0 \text{ Gy}$ photon boost); conventionally fractionated EBRT with photon boost ($25 \times 2.0 \text{ Gy} + 4 \times 5.0 \text{ Gy}$ photon boost); conventionally fractionated EBRT combined with HDR-BT; HDR-BT as monotherapy; and LDR-BT as monotherapy. Within each treatment type, we determined the number and proportion for categories of age, diagnosis period, Charlson comorbidity index (CCI), mode of detection, Gleason grade, clinical T, N and M stage, and time between diagnosis and primary radiation treatment. Likewise, medians and interquartile ranges were determined for total serum PSA, PSA density and proportion of positive cores at diagnosis, according to radiotherapy type. Trends in the types of radiotherapy delivered since 1998 are presented graphically as a percentage of all men who underwent primary radiotherapy. To provide context for trends in RT, we also describe the proportion of men receiving different primary treatments [i.e. RP, RT, ADT, and observation including AS and watchful waiting (WW)] for all men diagnosed with PCa from 1998 to 2016.

Variations in contemporary patterns of primary RT across counties were investigated for men diagnosed between 2012 and 2016. The proportion of men from each county who received conventionally fractionated EBRT, hypofractionated EBRT, EBRT with HDR-BT boost and LDR monotherapy were calculated using the total number of PCa cases diagnosed within each county from 2012 to 2016 as the denominator.

PCa-specific survival following primary radiotherapy was assessed using Kaplan–Meier methods, with survival time calculated from the start of treatment and censoring at the date of death from other causes or end of follow-up (31 December 2017). Cox proportional hazards regression was used to compare PCa-specific mortality among men diagnosed 2008–2016 with those diagnosed 1998–2007. Multivariable models were undertaken to adjust for age, Gleason grade, PSA level and clinical T-stage at diagnosis and mode of detection.

**Results**

The pathway for selection of the primary radiotherapy cohort is shown in Supplementary Figure S1. Of the 22,939 men with records in NPCR indicating radiotherapy as the initial treatment, 20,876 were validated as having received radiotherapy at doses and within time frames deemed reflective of primary radical therapy. Among men who had primary RT between 1998 and 2017, 51% received conventionally fractionated EBRT (total dose 60–82 Gy), while 11% received hypofractionated EBRT, 27% received EBRT with HDR-BT boost, 4% received LDR-BT and 2% HDR-BT monotherapy. Primary treatment via EBRT with photon or proton boost occurred in 2% of the cases, respectively (Table 1). Clinical characteristics varied across the treatment modalities, with those receiving EBRT generally being older and having more advanced disease at diagnosis than those who received brachytherapy monotherapies. Men who received photon boost or HDR-BT boost along with EBRT had more advanced disease than those receiving conventionally fractionated EBRT. The proportion of men receiving hypofractionated EBRT or photon boost therapy increased during the study period while the proportion receiving EBRT plus HDR–BT declined.

Use of ADT in conjunction with various primary radiotherapy modalities is presented in Supplementary Table 1, for the period since ADT data were available, i.e. 2006–2016. ADT was rarely given in conjunction with brachytherapy monotherapies since these treatments are mostly used for low-risk PCa. However, neoadjuvant ADT was commonly combined with hypofractionated EBRT (54%), EBRT with HDR (73%), and EBRT with photon or proton boost (59%). The majority of men receiving these types of RT also received adjuvant ADT.

Trends in patterns of radiotherapy over time, according to risk categories, are illustrated in Figure 2. As expected, radiotherapy types differed markedly for low-risk PCa compared with intermediate and high-risk categories. LDR-BT
monotherapy (and to a lesser extent HDR-BT monotherapy) accounted for one-third of radiation therapies delivered to men with low-risk disease but was infrequently used in intermediate and high-risk PCa. In contrast, almost all radiation therapy for intermediate and high-risk disease involved EBRT or EBRT combined with HDR-BT. During the most recent period, approximately 55% of men received dose-escalated EBRT (total dose ≥74 Gy). The remainder received hypofractionated EBRT or conventionally fractionated EBRT with HDR-BT boost. EBRT, with either photon or proton boost, was delivered to only a small proportion of men with PCa but appeared to be offered equally across different risk categories.

Trends over the past 20 years show an increase in conventionally fractionated total EBRT dose to the now standard of 78 Gy, as well as an increase in the use of hypofractionation,
across all risk categories. Except for LDR-BT, which has increased among men with low-risk disease, brachytherapy use (mono or combined) has declined over the past two decades.

The overall patterns of primary treatments of PCa over for men with non-metastatic PCa for the same period are shown in Supplementary Table 2. The proportion of men receiving primary RT for high risk and locally advanced PCa (i.e. N1) has increased over the past two decades but remained constant for intermediate-risk disease. Similar trends are also noted for RP. Meanwhile, the proportion of men with low-risk PCa who received RT has declined, with a corresponding increase in AS/observation.

Variations in patterns of primary radiotherapy by county are illustrated in Figure 3. EBRT was more common in northern Sweden, while the highest rate of EBRT combined with HDR-BT were observed among men in the Uppsala-Örebro health region. LDR-BT was predominantly offered to men residing in two specific counties but was rarely given to men residing in other counties.

Figure 4 shows the risk of PCa death following primary radiotherapy by risk category, comparing men diagnosed 1998–2006 with those diagnosed 2007–2016. Improvements in PCa survival are apparent across all risk categories. Crude hazard ratios (HR) and 95% confidence intervals (CI) when comparing men diagnosed in the later period with those diagnosed earlier were 0.54 (0.24–1.22); 0.66 (0.49–0.88); 0.87 (0.74–1.02) for low, intermediate and high-risk disease, respectively. Risk reductions remained after adjustment for age, Gleason grade, clinical T-stage, PSA and mode of detection for intermediate (HR: 0.72; CI 0.46–0.87) and high risk (HR: 0.72; CI 0.61–0.86).

**Discussion**

This study provides a description of definitive radiotherapy delivered in a nationwide population-based cohort of men with non-metastatic PCa in Sweden over two decades. There were strong temporal changes in type and dose of radiotherapy provided to men with PCa. In particular, there was increased use of dose escalation and hypofractionation across all risk categories, while use of EBRT with HDR-BT decreased. There were also large geographical variations in type of primary radiotherapy of PCa. PCa-specific survival improved in the latter compared with the earlier period.

Overall, current Swedish practice with regard to primary radiotherapy appears to be consistent with European [18] and American guideline [19] for the management of localised and locally advanced PCa. These guidelines endorse LDR-BT as an acceptable primary therapy for low-risk disease, if radical treatment is preferred over AS. However, use of BT monotherapy is discouraged for men in intermediate or high-risk categories (except for selected ‘favourable’ intermediate-risk disease). Both dose escalated EBRT (combined with short or long-term ADT) and EBRT plus HDR-BT boost, are recommended as suitable radiation therapies for intermediate or high-risk disease. In contrast, proton beam therapy/boost is currently considered to be an experimental
therapy, despite its potential to reduce toxicity [20]. Indeed, several radiotherapy centres across Sweden were engaged in a randomised trial of ultra-hypofractionated versus conventionally fractionated EBRT during the study period, in which approximately 500 Swedish men were randomised to the hypofractionated arm [9].

The trend towards higher dose and lower number of fractions (through hypofractionation or through HDR-BT boost) indicates early uptake in Sweden of radiotherapy techniques that deliver a potentially more biologically effective dose. There is mounting evidence indicating equivalent or better outcomes for dose escalation, moderate hypofractionation.
and combined EBRT/BT compared with conventionally fractionated EBRT. Several randomised trials [5,21,22] and meta-analyses [23] have shown improved outcomes for dose-escalated EBRT with respect to biochemical recurrence but not for overall survival. However, one large retrospective study has reported a survival benefit for men with intermediate and high-risk PCa, but not for low-risk disease [24]. Results from several large randomised trials of moderate and ultra-hypofractionation have demonstrated equivalent outcomes compared to conventionally fractionated EBRT for PCa-free survival, with acceptable levels of overall toxicity [7–9,25,26]. In addition, superior outcomes have been reported for HDR-BT in combination with EBRT compared with conventionally fractionated EBRT [27,28].

For low-risk disease, use of EBRT with HDR-BT boost decreased substantially while use of LDR-BT monotherapy increased over the past two decades. This likely represents a trend towards less aggressive treatment in men with low-risk disease, in whom disease tends to be indolent or progresses very slowly [29]. These changes do not necessarily indicate an overall increase in the use of BT for low-risk disease, but rather show changes in proportions among those who received primary radiotherapy. Radiotherapy for low-risk disease is likely to have decreased overall, due to high rates of adherence to 2013 Swedish guidelines update which strongly recommend AS for low-risk PCa [30].

Likewise, the high proportion of men who received neo-adjuvant or concurrent/adjuvant ADT in conjunction with EBRT over the past decade accords with current evidence and guidelines. Improvements in both disease specific and overall survival have been demonstrated in trials comparing EBRT combined with neo-adjuvant and adjuvant ADT to EBRT alone for localise PCa [31,32] and locally advanced disease [33]. It is now recommended that adjuvant ADT be offered in combination with EBRT for intermediate-risk (short-term) and high risk (long-term) PCa [18,19].

Substantial regional variation in the use of radiotherapy modalities was evident across Sweden. Similar disparities have been reported in other countries [34,35]. Regional variation is likely to be related to the location of radiotherapy centres and resulting referral patterns. For example, the LDR-technique is only implemented and available in Stockholm, Jönköping and Lund. In addition, differences may reflect preferences of the radiation oncologists within different centres serving specific counties, and for the degree to which they are engaged with academic research. For instance, delivery of moderately hypofractionated EBRT requires experienced teams and high-quality IGRT equipment [20], which may not be available in all treatment centres, while some academic centres have been involved in evaluating more experimental treatments (e.g. EBRT with proton boost [36]; ultra-hypofractionation [9]). However, the extent of regional variation found raises questions about whether men have equal access to therapies appropriate to their disease characteristics. This warrants further investigation.

Finally, we observed reductions in PCa-specific mortality among men diagnosed in 2007–2016 compared with 1998–2007 (i.e. 28% lower for intermediate and 37% lower for high-risk disease). These apparent improvements may be due to increased use of newer radiotherapy treatment regimens across Sweden, which have demonstrated superior survival outcomes [7,8,24–26]. It is also possible that greater use of endocrine therapy in conjunction with radiotherapy has contributed to improved outcomes, as demonstrated in the SPCG-7 trial [37,38], though we did not have data on endocrine therapy for a sufficient period to specifically examine trends in ADT. In addition, changing pathological criteria for grading and staging PCa over the study period likely have accounted for some of the apparent improvement [39]. The lack of statistically significant findings for low-risk PCa most likely reflects the low number of PCa deaths among men with predominantly indolent disease for whom radiotherapy has little to offer [29].

**Strengths, limitations and opportunities**

A major strength of PCBaSe is that it is a comprehensive and detailed clinical register with near complete capture of all PCa cases diagnosed in Sweden since 1998. The accuracy and validity of data items within NPCR has been assessed to be high and therefore the level of ascertainment of men who underwent primary radiotherapy is also likely to be high. Further capacity to check the validity of treatment classification was possible through linkage with data from hospital and drug registers. Moreover, the collection of detailed data on dose and fractions of radiotherapy delivered, along with comprehensive data for clinical characteristics and outcome, with linkages to drug and patient registers, provide a rich resource for further research on the real-world data.

Several limitations in the radiotherapy data collection warrant noting. Firstly, the retrospectively collected data are incomplete for some specific radiotherapy related data fields, particularly for disease characteristics immediately prior to secondary radiotherapy. Furthermore, data are not collected on dose to normal tissue which would be important for detailed studies on adverse effects due to radiotherapy. In addition, there is likely to be incomplete capture of secondary radiotherapy between 2008 and 2015, due to inconsistent reporting from radiotherapy centres during this period. Capture and completeness of post-operative/pre-radiotherapy data items have improved during the most recent period. However, the length of follow-up is currently quite short for some radiotherapy data items, limiting their use for assessing long-term outcomes. Transparent publicly available online reporting of all radical treatments in Swedish and English has been established to ensure continuing value of this resource [40]. Also, ongoing work on a national basis investigating the possibility to automatically transfer detailed radiotherapy data (dose-volume histograms) on target volumes and organs at risk from all radiotherapy centres in Sweden to a national radiotherapy register with the aim or linking to NPCR [41].

Custodians of PCBaSe invite clinicians and researchers with an interest in radiotherapy and PCa to undertake collaborative research using this resource. More information about the NPCR and PCBaSe is found at [www.npcr.se](http://www.npcr.se) and [www.pcbase.se](http://www.pcbase.se).
applications to the reference group can be submitted to par.stattin@surgsci.uu.se.

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