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Research Article

Does the CoreTherm®Concept Offering Transurethral Microwave Temperature Feedback Thermotherapy or Transurethral Resection of Prostate for Benign Obstruction have an Impact on Long-term Risk for Prostate Cancer Incidence and Mortality? Results from a Long time Nationwide Observational Cohort Investigation

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ABSTRACT

Background and Hypothesis: Intraprostatic hyperthermia <45° beyond ablation necrosis at ≥45° during CoreTherm® Concept (CT) treatment, a further developed TUMT, for benign prostate hyperplasia (BPH) may influence prostate cancer-related occurrence and death later in life.

Objective: To assess the risk of prostate cancer morbidity and mortality in men with BPH following thermotherapy/hyperthermia and transurethral resection of the prostate (TURP).

Design, Setting, and Participants: A nationwide, population-based study 1999-2019 in Sweden based on the Patient Register to identify cases of CT treatments (n= 4,686) and TURP (n= 74,527). Incident cases of prostate cancer were identified by linkage to the National Cancer Register.

Outcome Measurements and Statistical Analysis: Prostate cancer diagnosis and cancer-related mortality were the main outcome measures. Risks were calculated using hazard ratios (HRs) with a 95% Confidence interval (CI).

Results and Limitations: CT did not decrease the overall risk of being diagnosed with prostate cancer compared to TURP (HR 0.91, CI 0.79-1.04). For men above median age (71 years), CT decreased the risk for prostate cancer overall (HR 0.77, CI 0.64–0.92) and prostate cancer-specific death in the short-term (HR 0.51, 95% CI 0.32-0.83), long-term (HR 0.48, 95% CI 0.26-0.90) and overall (HR 0.66, 95% CI 0.49-0.87) compared to TURP. Age at intervention, age at diagnosis, and age at prostate cancer-related death did not differ significantly between the treatment groups overall.

Conclusions: Among men treated after 71 years of age CT for BPH was associated with an overall lower risk for a prostate cancer diagnosis later in life and a significantly decreased risk for prostate cancer-related death compared to TURP.

Patient Summary: Among elderly men with BPH, CT shows a decreased risk for prostate cancer and related death, compared to TURP in this national survey. However, a better definition of these retrospective cohorts is warranted before CT can be compared and adopted as a prevention strategy for prostate cancer.

Keywords: Benign Prostatic Hyperplasia (BPH); Incidental Prostate Cancer; Prostate Cancer Incidence and Mortality; CoreTherm® Concept(TUMT); Transurethral Resection of the Prostate (TURP); National Long-Time Observational Register Study.

INTRODUCTION

Benign prostate hyperplasia (BPH) is characterized by a histologically non-malignant hypertrophy of the adenomatous prostatic tissue surrounding the urethra. A recent systematic review found that the estimated lifetime prevalence of BPH was 26.2% and the condition is closely related to advancing age [1]. A large, long-time register study from Denmark has shown that clinical BPH, contrary to the general perception, is associated with a 2-3-fold increased risk of developing prostate cancer later in life [2]. BPH may give rise to a variety of lower urinary tract symptoms which are more likely to occur in men with a clinically enlarged prostate gland. Current medical treatment of lower urinary tract symptoms associated with BPH, may slow disease progression, and provide symptom relief [3]. Nonetheless, many patients will eventually require de-obstruction by active treatment or surgical intervention to alleviate symptoms and improve quality of life [4].

When invasive treatment for BPH is considered necessary, transurethral resection of the prostate (TURP) remains the mainstay of surgery. However, other procedures are available including the CoreTherm® Concept (CT) (transurethral microwave temperature feedback thermotherapy after intraprostatic injections of local anesthesia and Adrenaline). BPH is non-malignant but may coexist with incidental prostate cancer which is found in 3-16% of prostate specimens following BPH surgery [5,6]. Epidemiological studies also suggest an association between BPH and prostate cancer later in life with register-based data showing approximately 8% prostate cancer mortality among men having had BPH surgery [7-9].

Thus, non-radical invasive treatments for BPH, such as CT, may eliminate or diminish incidental prostate cancer and related incidence and death later in life. This nationwide, population-based cohort study aimed to assess the risk of prostate cancer incidence and mortality in men with BPH following CT vs. TURP.

MATERIALS AND METHODS

Data Sources

The study used data from nationwide registers for which reporting is mandatory, regulated by law, and supervised by the Swedish Board of Health and Welfare (*http://www.socialstyrelsen.se/english*). Register linkage based on the individually unique national registration number was used to ascertain information on exposures and outcomes. Exposed men were identified using the Patient Register, established in 1964, which contains data on individual hospital discharges including date and diagnoses according to the International Classification of Diseases (ICD) versions 7 through 10 and operation codes according to the Swedish Classification of Operations and Major Procedures. Correct coding for surgical procedures is achieved in 98% of cases [10].

Incident cases of prostate cancer were identified in the Swedish Cancer Register. The register, established in 1958, includes histologically verified incident cancers and is uniformly classified according to ICD versions 7-10. Classification of

tumour morphology using the Systematized Nomenclature of Medicine (SNOMED) is available from 1993. Cancer staging is based on the TNM - classification according to the Union for International Cancer Control (UICC) 2009 and is reported by the clinician at the time of diagnosis. The study was approved by the Research Ethics Committee Karolinska Institute, Stockholm, Sweden, and conforms to the STROBE guidelines for reporting observational studies (*www.strobe-statement.org*).

Study Design

From the Patient Register all men having undergone either TURP or CT from 1 January 1999, through 31 December 2019, were identified with the date of surgery/treatment used as a time of exposure. The Swedish Classification of Operations and Major Procedures were used to identify cases of TURP (code KED22) and CT (code KED72). Using individually unique national registration numbers, assigned to all Swedish citizens at birth or immigration, exposed men were linked to the Cancer Register and Cause of Death Register. Men having had more than one prostate procedure for BPH (n=1,256) or a diagnosis of prostate cancer at any time before or within one year of the exposure (n=15,326) were excluded from follow-up. Non-exposed were identified in the Cause of Death Register as men with a prostate cancer-related death but no record of TURP or CT in the Patient Register.

Incidence of prostate cancer was defined as the first registration of any prostate cancer in the Cancer Register (ICD-10 code C61) following exposure. Prostate cancer-specific death was assessed from the Cause of Death Register and for the outcome we only included deaths with prostate cancer as the primary cause of death. For men with other causes of death, the survival time was calculated until the death date according to the Cause of Death Register, and for men who were alive for the duration of the observation period, survival time was calculated from intervention until the end of the observation period. Person-time at risk was calculated beginning one year after the date of exposure until the first occurrence of prostate cancer or prostate cancer-related death.

Statistical Analysis

We calculated crude incidence rates for prostate cancer as the number of events per 100,000 person-years, with 95% confidence intervals (CIs) based on the Poisson distribution. Only the first occurrence of prostate cancer or prostate cancer-related death in everyone was counted as an event from one year after exposure. Risk of prostate cancer diagnosis and mortality after intervention were calculated by hazard ratios (HRs) using Cox proportional hazard models presented as HRs with 95% CIs. The age-adjusted risk for prostate cancer diagnosis was estimated using a proportional hazards assumption based on Schoenfeld residuals. Incidence rates and hazard ratios were calculated for three follow-up periods (Short-term): 1-5 years after intervention; 6-10 years after intervention; and (Long-term) >10 years after intervention and for the overall material. We used the median age at the time of intervention to categorize the effects of age on the associations. Survival from the

	CT N= 4,686	TURP N= 74,527	Non-exposed	CT vs. TURP	CT vs. non-exposed	TURP vs. non-exposed
No. of cases with prostate cancer	216 (4.6%)	4,574 (6.1%)	157,136	p< 0.001	p< 0.001	p< 0.001
Age at intervention (years)	71.3	70.3	NA	p= 0.09	NA	NA
Age at diagnosis of prostate cancer (years)	77.6	77.6	75.8	CI -1.52-1.52	CI 0.26-3.23	CI 1.39-2.10
No. of prostate cancer related deaths	59 (1.2%)	1,653 (2.2%)	26,830 (17.1%)	p< 0.001	p< 0.001	p< 0.001
Age at prostate cancer related death (years)	84.6	81.4	80.2	CI 0.34-5.98	CI 1.62-7.17	CI 0.70-1.78

Table 1: Cohort characteristics.

*Non-exposed were identified in the Cause of Death Register as men with prostate cancer-related death but no record of TURP or CT in the Patient Register.

time of intervention until the first diagnosis of prostate cancer diagnosis or prostate cancer-related mortality was compared by Kaplan-Meier survival analysis. Statistical analyses were performed using commercially available software (STATA and SPSS, version 9.1, SAS Institute, Cary, North Carolina).

RESULTS

The study cohort that was eligible for analysis consisted of 4,686 men having had CT, and 74,527 men having had TURP, contributing an accumulated 33,383 and 623,849 person-years of follow-up respectively. As shown in Table 1, the final study population included 216 cases of prostate cancer in the CT group, 4,574 cases in the TURP group, and 157,136 cases among the non-exposed. Age at intervention, age at diagnosis, and age at prostate cancer-related death did not differ significantly between the treatment groups overall. Men in the TURP group were significantly older compared to those non-exposed at the time of diagnosis (95% CI 1.39-2.10) whereas men in the CT group were significantly older than non-exposed at the time of prostate cancer-related death (95% CI 1.62-7.17).

Prostate cancer incidence rates are presented in Table 2. There was an overall significant difference in prostate cancer incidence rates between CT and TURP (-92.30. CI -183.93 – 0.66) and between CT and TURP among men above median age (-214.86 (CI -333.90 - -95.83) but not among men below median age (26.63, CI -118.03 – 171.30). The highest prostate cancer incidence rates were observed during the first five years after intervention for CT and TURP alike. The age-adjusted risk for prostate cancer diagnosis showed no significant difference in the first five years after intervention (HR 0.95, 95% CI 0.79-1.15), and borderline significant risk estimates year 6-10 (HR 0.76, 95% CI 0.59-0.98), after 10 years (HR 0.52, 95% CI 0.52-1.01), as well as overall (HR 0.74, 95% CI 0.74-0.98).

Table 3 shows the risk for prostate cancer diagnosis and death after CT about TURP over time. There was a non-significant overall decreased risk for a prostate cancer diagnosis following CT vs. TURP. For men below median age CT did not decrease the risk for a prostate cancer diagnosis at either short or long term. However, for those with an age above the

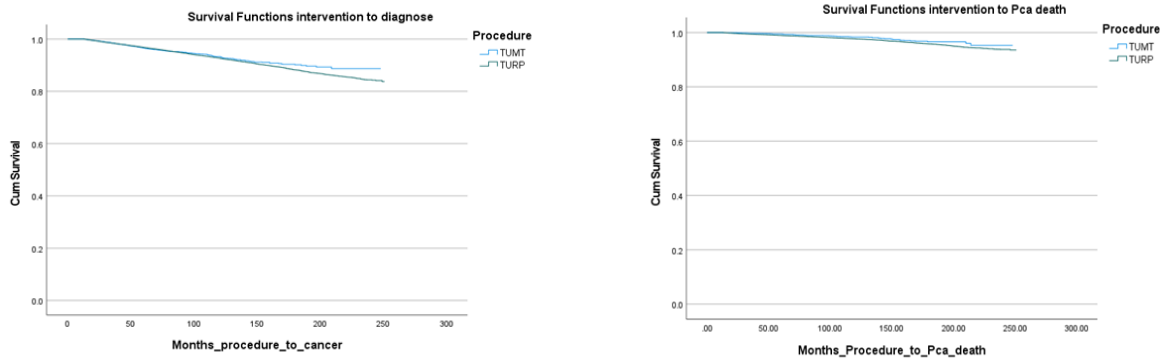

Figure 1: Kaplan-Meier survival plots for number of months from intervention to (a) prostate cancer diagnosis and (b) prostate cancer related death, as survival functions.

	No. of cases†	Year 1-5	Year 6-10	Year >10	Overall
CT	4,570	645	289	200	667
CT<median age	1,494	709	343	214	713
CT≥median age	3,076	612	250	183	633
TURP	71,243	625	369	287	759
TURP <median age	34,093	479	353	310	686
TURP ≥median age	37,150	768	388	247	848

Table 2: Prostate cancer incidence rates per 100,000 person-years following the first year after the intervention.

*Median age was 71 years.

†No. of cases reports number of CT and TURP procedures overall and categorized by median age.

	Year 1–5	Year 6–10	Year >10	Overall
Cancer Diagnosis				
All CT	1.06 (CI 0.89-1.29)	0.79 (CI 0.62-1.02)	0.72 (CI 0.52-1.01)	0.91 (CI 0.79-1.04)
CT <median age (71)	1.51 (CI 1.12-2.04)	0.94 (CI 0.66-1.34)	0.69 (CI 0.45-1.07)	1.04 (CI 0.85-1.28)
CT ≥ median age (71)	0.82 (CI 0.65-1.03)	0.66 (CI 0.46-0.94)	0.79 (CI 0.46-1.34)	0.77 (CI 0.64–0.92)
Death				
All CT	0.56 (CI 0.35-0.90)	1.12 (CI 0.74–1.70)	0.81 (CI 0.51-1.30)	0.79 (CI 0.61–1.67)
CT <median age (68)	0.79 (CI 0.33-1.67)	0.37 (CI 0.05-2.63)	1.66 (CI 0.81-3.40)	0.84 (CI 0.45-1.58)
CT ≥ median age (68)	0.51 (CI 0.32-0.83)	1.07 (CI 0.70–1.65)	0.48 (CI 0.26-0.90)	0.66 (CI 0.49-0.87)

Table 3: Risk of prostate cancer diagnosis (Hazard ratios) and prostate cancer related death for men having CT in relation to TURP.

*Patients that have died/ been diagnosed with prostate cancer within the first year of surgery have been censored from analysis.

	Subtype‡			Stage*			
	CT n= 157	TURP n= 3,612			CT n= 147	TURP n= 3,099	P-value
Adenocarcinoma other	9 (5.4%)†	116 (3.2%)	0.12	T1	67 (45.6%)	1,453 (46.9%)	0.76
Acinar adenocarcinoma	157 (94.6%)	3,495 (96.7%)	0.13	T2	50 (34.0%)	940 (30.3%)	0.34
Squamous cell carcinoma	0	0	N.A.	T3	26 (17.7%)	581 (18.7%)	0.75
Urothelial carcinoma	0	1 (0.03%)	N.A.	T4	4 (2.7%)	125 (4.0%)	0.43

Table 4: Histological subtypes and staging of prostate cancer in relation to CT and TURP.

‡ Cancer staging performed with the TNM-classification in accordance with UICC 2009 (amendments 2012). Clinical cancer stages were aggregated into T1, T2, T3 and T4.

*Clinical stage reported by clinician at the time of diagnosis.

† Includes two cases of intraductal and seven cases of other adenocarcinomas.

P-values calculated using chi-square statistics.

median, CT decreased the risk for a prostate cancer diagnosis 6-10 years after the intervention (HR 0.66, 95% CI 0.46-0.95), as well as overall (HR 0.77, 95% CI 0.62-0.92).

CT decreased the risk for prostate cancer-related death, in the short term (HR 0.56, 95% CI 0.35-0.90) and borderline overall (HR 0.79, CI 0.61-1-02). When considering age at intervention, there was no difference among men below median age but for men above median age CT decreased the

risk for prostate cancer-related death in short-term (HR 0.51, 95% CI 0.0.32-0.83), long-term (HR 0.48 95% CI 0.26-0.90) and overall (HR 0.66, 95% CI 0.49-0.87) compared to TURP.

Figure 1 presents Kaplan-Meier survival plots for the number of months from intervention to prostate cancer diagnosis and prostate cancer-related death. After CT(TUMT) the cumulative frequency without a registered prostate cancer diagnosis and prostate cancer-related death during the observational period was 95.3% and 98.7% respectively. For TURP the corresponding numbers were 93.6% and 97.8%. See supplemental for details on maximum length of survival (months).

The histologic character and staging of prostate cancer are presented in Table 4. The most common subtype of prostate cancer in both treatment groups was acinar adenocarcinoma. There were no significant differences between CT and TURP regarding histological subtypes or pathologic tumour staging at the time of diagnosis of prostate cancer.

DISCUSSION

The results of this nationwide population-based cohort study over 20 years suggest that among elderly men, CT doesn't seem to provide increased long-term risks for prostate cancer incidence or specific mortality. Overall, having had CT for BPH was not associated with a lower risk for a prostate cancer diagnosis later in life compared to men having had TURP. However, among men above 71 years of age, there was a significant decrease in prostate cancer risk after TUMT compared to TURP although the difference in risk was attenuated when more than 10 years had elapsed after the intervention. Age at the time of intervention was nearly identical between the treatment groups suggesting that the lower risk for prostate cancer after CT among the elderly was not explained by a higher prevalence of age-related incidental prostate cancer in the TURP group at the start of the observational period. There was also no significant difference between CT and TURP regarding age at diagnosis of prostate cancer.

There was an overall risk reduction for prostate cancer-related death after CT, but the difference was largely attributed to elderly men. When dichotomizing men with prostate cancer-related death according to median age at the time of intervention we found that elderly men carried a significantly lower risk for prostate cancer-related death following CT when compared to TURP. Thus, it appears that even though CT in general does not decrease the risk for prostate cancer, among the elderly it may be associated with decreased risk for prostate cancer-related morbidity and mortality later in life. The size of the study population did not allow for further age stratification due to the limited number of cases of prostate cancer in the CT group.

Compared to non-exposed men, prostate cancer-attributed mortality was lower for both CT and TURP. This concurs with another register-based study from Sweden showing a decreased risk for prostate cancer mortality following TURP compared to men with BPH having had no surgery [11]. Even though men having had CT were younger at the time of prostate cancer diagnosis compared to non-exposed, as well as, older at the time of prostate cancer-related death when compared to both men having had TURP and non-exposed, the differences were not significantly different. Even so, these observations support the overall findings of an eventual protective effect of invasive prostate treatments on cancer risk in men with BPH.

During the study period, the almost exclusive technique available for TUMT in Sweden was the CoreTherm® /PLFT® treatment with individualized energy dosage guided by temperature feedback (Prostalund AB, Sweden). The code for CT/TUMT used in the Classification of surgical procedures does not distinguish between various technique modality changes over time. Since 2004 all patients had CoreTherm® Concept treatment adding the intraprostatic injections of local anaesthetics + Adrenaline just before every thermotherapy. Blocked intraprostatic blood flow and secondary hypoxia during TUMT promote heat spread and secondary hyperthermia + lactic acidosis even to the peripheral zone. Theoretically, this can kill all or parts of incidental prostate cancer cells in the outer benign surviving prostate. For the first 5 years 1999 – 2004 the conventional CoreTherm® system with temperature feedback system (PLFT®) without local anaesthesia +Adrenaline was established. A minor part of all patients in the CT-treated cohort had no intraprostatic Adrenaline before treatment. CoreTherm® got American FDA approval in 2002, with minor statistical influence on the risk estimates. CT has been shown to provide short and long-term symptom relief comparable to the results seen after TURP [12,13], CT uses a urethral catheter to deliver high-energy microwaves to the prostate tissue which results in heat-induced coagulation necrosis in the central periurethral prostate. The CoreTherm Concept® was used in 20% of all de-obstructing active BPH procedures in Sweden last year (2023) and is expanding every year in Denmark. Heavily enlarged BPH can be treated with local anesthesia in an outpatient setup.

Despite the dearth of research to explain our findings, one may speculate on the mechanisms involved in an eventual decreasing the risk of prostate cancer diagnosis and death among elderly men with BPH following CT as compared to

TURP and non-exposed men. While coagulation diathermy used at TURP aims to control tissue damage and superficial bleeding, the disseminated prostate tissue damage provided by thermotherapy (>45°) heat conduction may be more effective at killing prostate cancer cells in the transition zone, and by hyperthermia (<45°) by convection spread in the peripheral zone, where many of the incidental cancers occur [14,15]. Extensive intraprostatic temperature mapping during PLFT®/CoreTherm® have verified hyperthermia >42° reaching the peripheral zone by heat conduction and convection [16]. This may trigger a cell-mediated immunologic antitumor response by exposing the cytoplasm and nuclear antigens in disintegrating cancer cells. Both BPH and prostate cancer have immunological components and an eventual lower risk for prostate cancer diagnosis, morbidity, and death after CT among the elderly. Complementary studies are needed to explain, by an augmented stimulation of anti-carcinogenic immune response to a prostate cancer antigen, an eventual protective effect in developing tumors when compared to TURP [17].

Inflammation is another potential mechanism of action by which CT could decrease the risk of prostate cancer when compared to TURP. Chronic inflammation can cause cancer in several organs including the liver, pancreas, and large intestine and increasing data suggest a role for inflammation also in the complex pathogenesis of prostate cancer. An inflammation of the prostate could influence molecular processes involved in prostate carcinogenesis such as DNA replication and interfere with cell-mediated cancer defenses.18 This notion is, however, challenged by a large histopathological study of BPH specimens showing that inflammation at the time of TURP was not associated with prostate cancer risk [11][17-23]. Nonetheless, our data suggest that TUMT may interact with one or several of the above-mentioned pathways to decrease the risk of prostate cancer over time compared to TURP.

How, and why, this relates to age at the time of intervention is unknown, and further studies are needed to verify and disentangle the involved mechanisms to better understand the results of the present observation. Considering that several of the associations had confidence intervals of borderline significance we recognize that a larger study population having had treatment with CT could have reinforced some of the observed trends i.e., that the associations had insufficient statistical power among younger men.

The use of national health care registers based on independently collected prospective data limits selection and ascertainment bias, whereas the use of a nationwide uniform classification of both exposure and outcome prevents classification bias. The validated registers supply scientific strength and minimize information and observation bias. To a certain degree, the diagnosis of the cause of death is subjective and a potential source of misclassification. However, this source of error is unlikely to be influenced by the type of prostate treatment a man has had earlier in life and thus would be a source of non-differential misclassification. To avoid misclassification of the exposure, patients having had more than one invasive prostate treatment were excluded from the analysis. Furthermore, we censored the longitudinal follow-up the first year after surgery/treatment to avoid detection bias. On a hypothetical basis, all cases of incidental prostate cancer were excluded after TURP but remained undetected in the CT cohort in this study. Incidental prostate cancer pT1 is a major problem with a bad prognosis according to three large, long-time follow-up national register studies [2,9,23].

Despite the strengths of our study, the use of diagnosis-based register data has some important limitations. Typically, an intrinsic limitation of using nationwide medical registers is the lack of information on lifestyle factors and an eventual significant co-morbidity in men with BPH influencing surgical decisions. Comorbidity patients will be selected for CT to a larger extent which is a less invasive procedure. This notion is supported by the significantly higher risk of death from lung cancer within the first five years after CT, as compared to TURP.

CONCLUSION

Among men treated after 71 years of age with CT for BPH, this observation study shows an overall lower risk for a prostate cancer diagnosis later in life and a significantly decreased risk for prostate cancer-related death compared to TURP. Even though the male population in Sweden is relatively homogenous, which increases the internal validity of the findings, an observational study design cannot infer causality. A careful interpretation and better understanding of the study results are therefore warranted before CoreTherm®Concept (TUMT) can be adopted as part of a prevention strategy for prostate cancer. The results strongly impose an ethical indication for further prospective high-quality studies on this matter.

COMPETING INTERESTS

Dr. Schelin S, M.D, Ph.D is the inventor of the CoreTherm® Concept. The other authors declare no competing interests.

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