Prostate Cancer

Characteristics of Patients in SPCG-15—A Randomized Trial Comparing Radical Prostatectomy with Primary Radiotherapy plus Androgen Deprivation Therapy in Men with Locally Advanced Prostate Cancer

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Abstract

Background: There is no high-grade evidence for surgery as primary treatment for locally advanced prostate cancer. The SPCG-15 study is the first randomized trial comparing surgical treatment with radiotherapy.

Objective: To describe the baseline characteristics of the first 600 randomized men in the SPCG-15 study. The study will compare mortality and functional outcomes.

Design, setting, and participants: This study is a Scandinavian prospective, open, multicenter phase III randomized clinical trial aiming to randomize 1200 men.

Intervention: Radical prostatectomy with or without consecutive radiotherapy (experimental) and radiotherapy with neoadjuvant androgen deprivation therapy (standard of care).

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Outcome measurements and statistical analysis: Cause-specific survival, metastasis-free survival, overall survival, and patient-reported bowel function, sexual health, and lower urinary tract symptoms were measured.

Results and limitations: The distribution of characteristics was similar in the two study arms. The median age was 67 yr (range 45–75 yr). Among the operated men, 36% had pT3a stage of disease and 39% had pT3b stage. International Society of Urological Pathology grades 2, 3, 4, and 5 were prevalent in 21%, 35%, 7%, and 27%, respectively. Half of the men (51%) in the surgery arm had no positive lymph nodes. The main limitation is the pragmatic design comparing the best available practice at each study site leading to heterogeneity of treatment regimens within the study arms.

Conclusions: We have proved that randomization between surgery and radiotherapy for locally advanced prostate cancer is feasible. The characteristics of the study population demonstrate a high prevalence of advanced disease, well-balanced comparison groups, and a demography mirroring the Scandinavian population of men with prostate cancer at large.

Patient summary: This study, which has recruited >600 men, compares radiotherapy with surgery for prostate cancer, and an analysis at the time of randomization indicates that the study will be informative and generalizable to most men with locally advanced but not metastasized prostate cancer.

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1. Introduction

Prostate cancer mortality has declined significantly over the past 15 yr, mainly due to earlier detection and treatment through opportunistic testing with prostate-specific antigen (PSA) [1]. Around 3.5–5% of men diagnosed with prostate cancer are diagnosed with a locally advanced, defined as stage T3 or T4, nonmetastatic cancer [2,3]. Locally advanced prostate cancer is associated with a high risk of progression and subsequent prostate cancer mortality [4].

In contrast to other major cancer forms, there has been a long-standing lack of multimodal cancer treatments for locally advanced prostate cancer. For a long time, there was no evidence-based curative treatment, and many men with locally advanced nonmetastatic prostate cancer were treated conservatively with androgen deprivation therapy alone [4]. In 2009, the SPCG-7 trial reported a clear benefit of radiotherapy with androgen deprivation therapy in men with mainly locally advanced prostate cancer, compared with androgen deprivation therapy alone, and the findings have since been corroborated further by two additional randomized trials [5–7].

While there is evidence from randomized trials for survival benefit of surgery in localized prostate cancer, and data from observational cohorts support radical prostatectomy as treatment for locally advanced disease, there is yet no randomized controlled trial comparing primary surgery with primary radiotherapy for men with mainly locally advanced prostate cancer [7–18].

SPCG-15 is a Scandinavian multicenter, randomized, open phase III trial in which patients are randomized 1:1 either to primary radiotherapy including androgen deprivation or to primary radical prostatectomy with optional postoperative radiotherapy [19].

Here, we present the baseline characteristics and pathology data from the prostatectomy specimen of the first 600 patients. Our aim is to describe the characteristics of the study cohort to assess future generalizability.

2. Patients and methods

SPCG-15 is a prospective, multicenter, open, randomized phase III trial including patients with locally advanced, stage T3 or T4 (according to either clinical examination or radiology; defined on magnetic resonance imaging [MRI] as a risk of extraprostatic extension of at least 4/5 on a Likert’s scale [20], N0 stage (defined in accordance to the RECIST guidelines [<1.5 cm long axis] [21], nonmetastatic (confirmed by bone scan, computed tomography, or MRI of axial skeleton, at a minimum of pelvis and lumbar vertebral column [22]) prostate cancer randomized either to radiotherapy with neoadjuvant as well as adjuvant (hereafter, for brevity, referred to as neoadjuvant) androgen deprivation (standard arm) or to radical prostatectomy followed by salvage radiation or endocrine therapy if deemed indicated (experimental arm).

The randomization is done in blocks to ensure an even distribution within study sites. The study protocol has been described in more detail previously (for full inclusion and exclusion criteria, please see the article describing the SPCG-15 trial by Stranne et al. [19]). The total number of randomized patients aimed for inclusion in the study is 1200. The primary aim is to investigate whether radical prostatectomy with postoperative radiotherapy if needed improves prostate cancer–specific survival in comparison with primary radiotherapy plus androgen deprivation. Secondary aims are to compare metastasis-free and overall survival, quality of life, functional outcomes, and healthcare consumption in the two treatment arms.

Before randomization, patients fill out a study-specific quality-of-life questionnaire. The form was created using a “one concept, one question” method described in detail before by Steineck et al. [23], and adjusted after interviews with prostate cancer patients and tested for face validity.
The quality-of-life questionnaire comprises 118 questions concerning patient characteristics, demography, experience, psychological symptoms (anxiety and depression), sense of well-being, and quality of life, as well as physical symptoms (including urinary, bowel, and sexual functions), pain, and, in addition, symptoms regarding hormonal therapy, if applicable. This form is filled in at baseline as well as 1, 2, 5, 10, 15, and 20 yr after randomization. The questions investigate the quality, frequency, and intensity of each symptom and include a bother score. The quality-of-life and psychological parameters are measured on a visual digital scale from 1 to 7, where 1 and 2 are considered low intensity; 3, 4, and 5 moderate intensity, and 6 and 7 high intensity.

Follow-up, including laboratory tests and clinical examination, is documented using web-based case report forms including all data pertaining to primary and secondary endpoints. The case report forms are filled out by study nurses and investigators at each site.

The first patient was randomized in October 2014, and, as of May 23rd 2022 856 patients have been randomized. In the present analysis, we have chosen to describe the first 600 patients to avoid missing data due to latency in reporting.

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3. Results

Baseline demographic and social characteristics are presented in Table 1. The mean age at randomization was 67 yr (range 45–75 yr). Of the cohort, 66% are either over-
| Clinical baseline data                      | Prostatectomy (%) | Radiotherapy (%) | Total (%) |
|--------------------------------------------|-------------------|-----------------|-----------|
| Number of patients                         | 301 (100)         | 299 (100)       | 600 (100) |
| Previous active surveillance               |                   |                 |           |
| Yes                                        | 15 (5)            | 15 (5)          | 30 (5)    |
| No                                         | 268 (89)          | 263 (88)        | 531 (88)  |
| Missing                                    | 18 (6)            | 21 (7)          | 39 (7)    |
| PSA at inclusion (µg/l)                    |                   |                 |           |
| Median                                     | 13.0              | 11.0            | 12.0      |
| Interquartile range (25p–75p)             | 7.5–26.0          | 7.3–23.0        | 7.5–24.8  |
| % PSA >20                                  | 34                | 28              | 31        |
| Missing                                    | 0 (0)             | 0 (0)           | 0 (0)     |
| Clinical T stage (DRE)                     |                   |                 |           |
| T1                                         | 19 (6)            | 20 (7)          | 39 (7)    |
| T2                                         | 33 (11)           | 34 (11)         | 67 (11)   |
| T3                                         | 248 (82)          | 244 (82)        | 492 (82)  |
| T4                                         | 1 (0)             | 0 (0)           | 1 (0)     |
| Missing                                    | 0 (0)             | 1 (0)           | 0 (0)     |
| Imaging T stage (MRI)                      |                   |                 |           |
| No. of patients undergoing MRI             | 179               | 182             | 361       |
| T1                                         | 3 (2%)            | 1 (1%)          | 4 (1%)    |
| T2                                         | 6 (3%)            | 4 (2%)          | 10 (3%)   |
| T3                                         | 163 (91%)         | 167 (92%)       | 330 (91%) |
| T4                                         | 7 (4%)            | 10 (5%)         | 17 (5%)   |
| Missing                                    | 0 (0%)            | 0 (0%)          | 0 (0%)    |
| Prostate volume (cc)                       |                   |                 |           |
| Median                                     | 38.5              | 36.0            | 37.0      |
| IQ range (25p–75p)                         | 30.0–50.5         | 30.0–45.0       | 30.0–48.9 |
| % >50 cc                                   | 25                | 16              | 20        |
| Missing                                    | 17 (6)            | 20 (7)          | 37 (6)    |
| ISUP grade                                 |                   |                 |           |
| Grade group 1                              | 0 (0)             | 0 (0)           | 0 (0)     |
| Grade group 2                              | 78 (26)           | 76 (25)         | 154 (26)  |
| Grade group 3                              | 87 (29)           | 80 (27)         | 168 (28)  |
| Grade group 4                              | 49 (16)           | 62 (21)         | 111 (19)  |
| Grade group 5                              | 87 (29)           | 79 (26)         | 166 (28)  |
| Missing                                    | 0 (0)             | 2 (1)           | 2 (0)     |
| Biopsies                                   |                   |                 |           |
| No of coresb                              |                   |                 |           |
| 2–5                                        | 17 (6)            | 27 (9)          | 44 (7)    |
| 6–9                                        | 29 (10)           | 27 (9)          | 56 (9)    |
| 10–14                                      | 238 (79)          | 235 (79)        | 473 (79)  |
| >15                                        | 6 (2)             | 2 (1)           | 8 (1)     |
| Missing                                    | 11 (4)            | 8 (3)           | 19 (4)    |
| Total biopsy length (mm)                   |                   |                 |           |
| <50                                        | 17 (6)            | 30 (10)         | 47 (8)    |
| 50–99                                      | 29 (10)           | 32 (11)         | 61 (10)   |
| 100–199                                    | 208 (69)          | 189 (63)        | 397 (68)  |
| >200                                       | 20 (7)            | 26 (9)          | 46 (8)    |
| Missing                                    | 27 (9)            | 22 (7)          | 49 (8)    |
| Number of cores with cancer                |                   |                 |           |
| 1–4 biopsiesc                            | 60 (20)           | 82 (27)         | 142 (24)  |
| 5–9 biopsies                              | 147 (49)          | 144 (48)        | 291 (49)  |
| ≥10 biopsies                              | 81 (27)           | 63 (21)         | 144 (24)  |
| Missing                                    | 13 (4)            | 10 (3)          | 23 (4)    |
| Total cancer length (mm)                   |                   |                 |           |
| <20                                        | 44 (15)           | 53 (18)         | 97 (16)   |
| 20–49                                      | 101 (34)          | 105 (35)        | 206 (34)  |
| 50–99                                      | 103 (34)          | 93 (31)         | 196 (33)  |
| 100–149                                    | 29 (10)           | 28 (9)          | 57 (10)   |
| >150                                       | 7 (2)             | 6 (2)           | 13 (2)    |
| Missing                                    | 17 (6)            | 14 (5)          | 31 (5)    |
| Charlson comorbidity indexd                |                   |                 |           |
| 0–2                                        | 29 (10)           | 33 (11)         | 62 (10)   |
| 3–4                                        | 228 (76)          | 220 (74)        | 448 (75)  |
| >4                                         | 29 (10)           | 33 (11)         | 28 (5)    |
| Missing                                    | 15 (5)            | 13 (4)          | 28 (5)    |

CCI = Charlson comorbidity index; DRE = digital rectal examination; IQ = interquartile; ISUP = International Society of Urological Pathology; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.

b % out of patients undergoing MRI.

c No points for prostate cancer in CCI tumor.

d % out of patients undergoing MRI.
Table 3 – Pathology data from the surgical specimen

| Postoperative data | Prostatectomy (%) |
|--------------------|-------------------|
| Number of patients | 301 (100)         |
| T stage (pT)       |                   |
| T2                 | 47 (16)           |
| T3a                | 107 (36)          |
| T3b                | 118 (39)          |
| T4                 | 2 (1)             |
| Missing            | 27 (9)            |
| ISUP grade         |                   |
| Grade group 1      | 2 (1)             |
| Grade group 2      | 62 (21)           |
| Grade group 3      | 106 (35)          |
| Grade group 4      | 22 (7)            |
| Grade group 5      | 82 (27)           |
| Missing            | 27 (9)            |

Lymph nodes

- Positive: 111 (37)
- Negative: 153 (51)
- Missing: 37 (12)

No. of positive lymph nodes

- 0 lymph nodes: 153 (51)
- 1–3 lymph nodes: 88 (29)
- >3 lymph nodes: 24 (8)
- Missing: 36 (12)

ISUP = International Society of Urological Pathology.

* Seventy-nine patients had both pT3b and positive lymph node status.

The men reported low to moderate scores for quality of life (Fig. 1). Of the patients, 3% reported urinary leakage at least once a day, 72% had nocturia up to two times nightly, and 76% stated no to little bother from lower urinary tract symptoms. In total, 74% and 51% of patients reported never experiencing constipation and loose stool ever, respectively. Of the patients, 57% reported having an active sex life with a partner, 62% stated erectile function sufficient for intercourse or masturbation, and 61% reported moderate to very good ability to achieve orgasm.

Table 4 – QoL data at baseline

| Quality of life data | Prostatectomy (%) | Radiotherapy (%) | Total (%) |
|----------------------|-------------------|-----------------|-----------|
| Number of patients   | 301 (100)         | 299 (100)       | 600 (100) |
| Baseline quality of life |
| Low intensity        | 13 (4)            | 4 (1)           | 17 (3)    |
| Moderate intensity   | 133 (48)          | 143 (48)        | 276 (46)  |
| High intensity       | 138 (46)          | 136 (45)        | 274 (46)  |
| Missing              | 17 (6)            | 16 (5)          | 33 (6)    |
| Meaningfulness       |
| Low intensity        | 5 (2)             | 2 (1)           | 7 (1)     |
| Moderate intensity   | 79 (26)           | 79 (26)         | 158 (26)  |
| High intensity       | 199 (66)          | 202 (68)        | 401 (67)  |
| Missing              | 18 (6)            | 16 (5)          | 34 (6)    |
| Mental well-being    |
| Low intensity        | 18 (6)            | 11 (4)          | 29 (5)    |
| Moderate intensity   | 136 (45)          | 148 (49)        | 284 (47)  |
| High intensity       | 128 (43)          | 125 (42)        | 253 (42)  |
| Missing              | 19 (6)            | 15 (5)          | 34 (6)    |
| Depression           |
| Low intensity        | 155 (51)          | 155 (52)        | 310 (52)  |
| Moderate intensity   | 108 (36)          | 111 (37)        | 219 (37)  |
| High intensity       | 20 (7)            | 17 (6)          | 37 (6)    |
| Missing              | 18 (6)            | 16 (5)          | 34 (6)    |
| Anxiety              |
| Low intensity        | 133 (44)          | 143 (48)        | 276 (46)  |
| Moderate intensity   | 122 (41)          | 108 (36)        | 230 (38)  |
| High intensity       | 27 (9)            | 32 (11)         | 59 (10)   |
| Missing              | 19 (6)            | 16 (5)          | 35 (6)    |

QoL = quality of life.
Patients answer question on a scale from 1 to 7, with 1–2 indicating low intensity, 3–5 moderate intensity, and 6–7 high intensity.

With the randomization of more than 800 men in the SPCG-15 study, we have proved the feasibility of a randomized trial comparing primary surgery with radiotherapy among men with locally advanced prostate cancer. After having randomized the first 600 men, we find balanced distribution of characteristics in the two study arms, and the enrolled men seem to well represent the target population of men with locally advanced cancer (eligible for both treatments) undergoing treatment with curative intent.

Although new treatments are being added to the armory of therapies for prostate cancer, to our knowledge, no new evidence has emerged disputing the need for this trial. The potential benefit of surgery in locally advanced prostate cancer remains unclear, and the rationale for this trial remains. The role of radiotherapy plus androgen deprivation therapy in this patient group is well established [5–7], and although several observational studies indicate an equal effect of radical prostatectomy—in addition to the SPCG-4 trial showing a clear benefit of radical prostatectomy among patients in whom postoperative upgrading is commonplace—a head-to-head comparison is imperative to provide best possible evidence-based care for this patient group [7–18,24].

Our study population so far presents men with high-risk features in terms of histopathology, clinical stage, and PSA.
Table 5 – Description of sex life and symptoms from the lower urinary tract and bowel at baseline

| LUTS, bowel, sex | Prostatectomy (%) | Radiotherapy (%) | Total (%) |
|------------------|-------------------|------------------|-----------|
| Number of patients | 301 (100) | 299 (100) | 600 (100) |
| **Urinary tract symptoms** | | | |
| Weak urine stream | | | |
| Never | 53 (18) | 75 (25) | 128 (21) |
| In less than half of the times | 105 (35) | 105 (35) | 210 (35) |
| In more than half of the times | 75 (25) | 60 (20) | 135 (23) |
| Always | 50 (17) | 42 (14) | 92 (15) |
| Missing | 19 (6) | 17 (6) | 35 (6) |
| Nocturia | | | |
| Never | 46 (15) | 44 (15) | 90 (15) |
| 1 per night | 118 (39) | 118 (39) | 236 (39) |
| 2 per night | 75 (25) | 63 (21) | 138 (23) |
| >3 per night | 10 (3) | 10 (3) | 20 (3) |
| Missing | 20 (7) | 18 (6) | 38 (6) |
| Nocturia | | | |
| Never | 46 (15) | 44 (15) | 90 (15) |
| 1 per night | 118 (39) | 118 (39) | 236 (39) |
| 2 per night | 75 (25) | 63 (21) | 138 (23) |
| >3 per night | 10 (3) | 10 (3) | 20 (3) |
| Missing | 20 (7) | 18 (6) | 38 (6) |
| Urinary leakage | | | |
| Never | 233 (77) | 243 (81) | 476 (79) |
| At least once per month or more | 25 (8) | 20 (7) | 45 (8) |
| At least once per week | 8 (3) | 12 (4) | 20 (3) |
| At least 3 times per week | 7 (2) | 3 (1) | 10 (2) |
| At least once per day | 7 (2) | 3 (1) | 10 (2) |
| At least 2 times per day | 2 (1) | 1 (0) | 3 (1) |
| Always | 0 (0) | 0 (0) | 0 (0) |
| Missing | 19 (6) | 17 (6) | 36 (6) |
| Urinary catheter | | | |
| Yes | 6 (2) | 6 (2) | 12 (2) |
| No | 271 (90) | 272 (91) | 543 (91) |
| Missing | 24 (8) | 21 (7) | 45 (8) |
| Overall bother | | | |
| No bother | 154 (51) | 148 (49) | 302 (50) |
| A little bother | 83 (28) | 71 (24) | 154 (26) |
| Moderate bother | 36 (12) | 40 (13) | 76 (13) |
| Considerable bother | 9 (3) | 19 (6) | 28 (5) |
| Missing | 19 (6) | 21 (7) | 40 (7) |
| Bowel symptoms | | | |
| Constipation | | | |
| Never | 216 (72) | 225 (75) | 441 (74) |
| At least once per month | 45 (15) | 40 (13) | 85 (14) |
| At least once per week | 17 (6) | 14 (5) | 31 (5) |
| At least 3 times per week | 2 (1) | 3 (1) | 5 (1) |
| At least once per day | 2 (1) | 0 (0) | 2 (0) |
| At least 2 times per day | 0 (0) | 0 (0) | 0 (0) |
| Always (almost) | 2 (1) | 0 (0) | 2 (0) |
| Missing | 17 (6) | 17 (6) | 34 (6) |
| Loose stool | | | |
| Never | 153 (51) | 154 (52) | 307 (51) |
| At least once per month | 59 (20) | 75 (25) | 134 (22) |
| At least once per week | 40 (13) | 34 (11) | 74 (12) |
| At least 3 times per week | 19 (6) | 11 (4) | 30 (5) |
| At least once per day | 3 (1) | 3 (1) | 6 (1) |
| At least 2 times per day | 2 (1) | 1 (0) | 3 (1) |
| Always (almost) | 8 (3) | 3 (1) | 11 (2) |
| Missing | 17 (6) | 18 (6) | 35 (6) |
| Sex life | | | |
| Ability to achieve erection | | | |
| Nonexistent | 45 (15) | 48 (16) | 93 (16) |
| Inadequate for any kind of sexual activity | 51 (17) | 45 (15) | 96 (16) |
| Sufficient for masturbation | 80 (27) | 73 (24) | 153 (26) |
| Sufficient for intercourse | 103 (34) | 114 (38) | 217 (36) |
| Missing | 22 (7) | 19 (6) | 41 (7) |
|Ability to achieve orgasm | | | |
| Very poor to nonexistent | 44 (15) | 41 (14) | 85 (14) |
| Poor | 50 (17) | 49 (16) | 99 (17) |
| Moderate | 75 (25) | 79 (26) | 154 (26) |
| Good | 68 (23) | 57 (19) | 125 (21) |
| Very good | 38 (13) | 47 (16) | 85 (14) |
| Missing | 26 (9) | 26 (9) | 52 (9) |
| Active sex life with partner | | | |
| Yes | 168 (56) | 176 (59) | 344 (57) |
| No | 111 (37) | 102 (34) | 213 (36) |
| Missing | 22 (7) | 21 (7) | 43 (7) |

LUTS = lower urinary tract symptoms.
Of the men in the surgery arm, 80% had no or fewer than four positive lymph nodes in the pathology specimen, and may thus be considered to have potentially curable disease [25]. A significant proportion of men in the surgical arm had pT3b, a disease stage known to be associated with particularly rapid progression to disseminated disease [26]. There is a risk that any difference in outcome between the treatment arms is diluted if a large proportion of men have too advanced disease to be potentially cured by the treatment. Our per-protocol, prespecified, stratified analysis by tumor substage and grade is therefore well justified to assess whether there are different effects of treatment in various subcategories not appearing in the overall analysis. There are currently no studies directly comparable with SPCG-15, as there are no randomized head-to-head comparisons of radiotherapy and surgery among men with locally advanced prostate cancer. When comparing the characteristics of our study population with previous cohorts from curative trials of the efficacy of surgery, our study includes the most advanced cases. In the SPCG-4 trial, where watchful waiting was compared with radical prostatectomy in the pre-PSA and pre-MRI era, pT3 disease was found in 46.5% of the radical prostatectomy patients as compared with 75% in our study thus far. A comparison of our cohort with the SPCG-4 cohort is relevant because SPCG-4 included men with palpatory T1c or T2 disease at baseline, which turned out to be pT3 in almost half the cases, similar to how we now include patients who show signs of T3 tumors on MRI but might have T1c or T2 according to digital rectal examination. While a majority of radical prostatectomy patients in both SPCG-4 and SPCG-15 had a postoperative Gleason sum of 7/ISUP 2 and 3 (55.2% and 56%, respectively), only 13.4% of SPCG-4 patients had a Gleason sum of 8–10, in contrast to 34% of SPCG-15 patients with ISUP 4 and 5 [24]. SPCG-15 patients seem to be presenting with advanced disease in comparison with the TROG 96.01 trial patients. On the contrary, the PIVOT trial, which also compared surgery with conservative treatment, was conducted in the PSA era, and it randomized mainly men with low-

**Fig. 1** – Bar charts showing baseline lower urinary tract, bowel, and sexual symptoms. LUTS = lower urinary tract symptoms; min = minimum; n = night.

**Fig. 2** – Pie chart showing T stage up- and downgrading rates preoperatively versus postoperatively.
risk disease with Gleason grade 6 pathology who, according to the guidelines of today, should have had active monitoring rather than treatment with curative intent.

With a similar median age of 67–68 yr (depending on treatment arm), in TROG 96.01, the patients had higher median PSA of 14.4–16.4 µg/l, with 33–43% having PSA of >20 µg/l, compared with 12 µg/l and 31%, respectively in our cohort. Notably, TROG 96.01 diagnostic biopsy Gleason scores were remarkably lower; 42–46% of patients in TROG 96.01 were diagnosed with Gleason 2–6 compared with 0% (as a result of the exclusion criteria) in SPCG-15, and 15–20% in TROG were diagnosed with Gleason 8–10 compared with 47% in SPCG-15. However, this is probably attributable to TROG 96.01 including patients with T2b and T2c tumors [7]. We acknowledge that the Gleason system has since been replaced with the ISUP system, making direct comparisons difficult. In summary, SPCG-15 is a cohort with such higher precision.

The anxiety and depression levels were increased compared with age-matched men in the general population of Sweden and England as well as Denmark [27–29], possibly with age-matched men in the general population of targeted with such high precision.

In summary, SPCG-15 is a cohort with such high precision.

The SPCG-7 trial, comparing radiotherapy plus long-term androgen deprivation therapy with life-long androgen deprivation therapy alone in locally advanced prostate cancer (80%) or cT2 with PSA >20 (20%), investigated a similar target group to the SPCG-15 trial, although SPCG-7 was conducted in the pre-MRI era, and results may not be automatically generalizable to all MRI-defined T3 tumors. The baseline quality–of-life characteristics in SPCG-7 and SPCG-15 trials appear to be similar in many ways. Regarding both lower urinary tract symptoms (including urinary leakage) and bowel symptoms, both cohorts present with very low scores, indicating good urinary function at baseline despite advanced tumors. The majority of SPCG-15 patients reported no-to-little bother due to lower urinary tract symptoms, which is comparable with the average of 2/10 on a bother score (where 10 represents maximum bother) in SPCG-7. The sexual function differs between the two cohorts at baseline: 36% of SPCG-15 men present with erectile function sufficient for intercourse, whereas in SPCG-7, the percentage of men was 47% in the androgen deprivation therapy group and 51% in the radiotherapy plus androgen deprivation therapy group [30].

Regarding education, marital status, and occupation, the SPCG-15 cohort correlates well with the general population for this age group in Sweden according to data from Statistics Sweden, the central bureau for statistics in Sweden [31–34]. The incidence of overweight (body mass index 25–29) is 47% in our cohort, at the same level as in England and slightly higher than that in the general population in the same age groups both in Sweden and Denmark (43% and 22%, respectively) [35,36].

Regarding physical activity, 53% of our patients exercised >3 h/wk as compared with 30% of men aged 65–84 yr in the general population of Sweden [37]. Smoking habits are slightly lower in the general population of Sweden; approximately 8% of men aged 65–84 yr smoke [38] compared with 13% of the men in SPCG-15. However, the general Danish population has a higher smoking prevalence (16.9%) in the age span of 65–74 yr, which probably accounts for the higher numbers in our cohort [39]. In the UK, 9% of men aged 65–74 yr smoke [40].

In summary, our data do not indicate any important deviance from age-equivalent male populations in Sweden, Denmark, and England, which would preclude generalizability at least to other Caucasian male populations [3].

It is our opinion that successful and speedy completion of this trial depends on adherence to national and/or European Association of Urology guidelines, and that radiotherapy with neoadjuvant hormonal treatment is the standard treatment of choice outside the trial, whereas surgical treatment is offered only as an experimental treatment within SPCG-15. Although this strategy may be considered controversial since surgery is already widespread in locally advanced prostate cancer, the current evidence basis is undoubtedly stronger for radiotherapy, and a head-to-head comparison is the only way to find out whether primary surgery leads to better outcomes.

### Table 6 – Primary treatment regimens in the two study arms

| Primary treatment regimens | Number of patients (%) |
|----------------------------|------------------------|
| Total number of patients receiving primary prostatectomy | 301 (100) |
| Surgical approach | |
| Retropubic prostatectomy | 39 (13) |
| Laparoscopic prostatectomy | 3 (1) |
| Robot-assisted laparoscopic prostatectomy | 232 (77) |
| Missing | 27 (9) |
| Lymph node dissection | |
| Yes | 258 (86) |
| No | 12 (4) |
| Missing | 31 (10) |
| Total number of patients receiving primary radiotherapy | 299 (100) |

### Table 7 – External beam radiotherapy regimens

| Total dose prostate (Gy) | Fraction size (Gy) | Number of patients (%) |
|--------------------------|-------------------|------------------------|
| 60–66 | 3 | 4 (2) |
| 72.5–77 | 2.3–2.7 | 7 (4) |
| 77 | 2.2 | 12 (7) |
| 74–78 | 1.8–2 | 141 (86) |
| All | All | 164 (100) |
We acknowledge that the two treatment arms are heterogeneous in terms of allowing different radiotherapy regimens (e.g., external beam radiation plus brachytherapy vs external beam radiation alone) as well as varying surgical approaches (e.g., open surgery vs robotic laparoscopic surgery, varying lymph node dissection approaches; Tables 6–8). This has been a pragmatic approach to make the study realizable since clinical practice differs substantially between centers. The principle of the study is to compare best practices available to the patient. We therefore consider this variability a strength for later generalizability. Nevertheless, due to continuous updates of treatment regimens and care processes, an inherent weakness of the study is the fact that the results may already be outdated when the cohort is mature for final analyses—a destiny to which all studies with long-term follow-up are doomed.

5. Conclusions

In summary, we are presenting a cohort with advanced prostate cancer disease with respect to both stage and grade. Altogether, our study population seems to well represent the Scandinavian population at large. SPCG-15 has demonstrated that randomization to surgery or radiotherapy is feasible in a population of men with locally advanced prostate cancer. We are two-thirds through its inclusion phase and are likely to be closed for further inclusion within 4 yr (Fig. 3).

Author contributions: Magdalena Gongora had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Brasso, Stranne, Akre, Petersen, Lilley, Mirtti, Jäderling, Bottai, Karlsson, Johansson, Jacobsen, Hansen, Rannikko, Olsson, Lindberg, Røder.

Analysis and interpretation of data: Gongora, Stranne, Brasso, Petersen, Lilley, Mirtti, Jäderling, Bottai, Karlsson, Johansson, Jacobsen, Hansen, Rannikko, Olsson, Lindberg, Røder.

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Statistical analysis: Gongora, Bottai.

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References
[1] Kvåle R, Møller B, Angelsen A, et al. Regional trends in prostate cancer incidence, treatment with curative intent and mortality in Norway 1980–2007. Cancer Epidemiol 2010;34:359–67.
[2] NPCR. Nationella Prostatacancerregistret (NPCR) (National Prostate Cancer Registry - Sweden). RATTEN. Diagnostik. Riskgruppsfördelning (detajerad). 2022.
[3] Partin AW, Dmochowski RR, Kavoussi LR, Peters CA, Wein AJ. Campbell Walsh Wein urology. ed. 12. Elsevier; 2020.
[4] Akre O, Garmo H, Adolfsson J, Lambe M, Bratt O, Stattin P. Mortality among men with locally advanced prostate cancer managed with noncurative intent: a nationwide study in PCBase Sweden. Eur Urol 2011;60:554–63.
[5] Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/ SFUO-3): an open randomised phase III trial. Lancet 2009;373:301–8.
[6] Mottet N, Peneau M, Mazeron JJ, Molinie V, Richard P. Addition of radiotherapy to long-term androgen deprivation in locally advanced prostate cancer: an open randomised phase 3 trial. Eur Urol 2012;62:213–9.
[7] Denham JW, Steiger A, Lamb DS, et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. Lancet Oncol 2011;12:451–9.
[8] Ward JF, Slezak JM, Blute ML, Bergstralh EJ, Zincke H. Radical prostatectomy for clinically advanced (ctT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. BJU Int 2005;95:751–6.
[9] Van Poppel H, Vekemans K, Da Pozzo L, et al. Radical prostatectomy for locally advanced prostate cancer: results of a feasibility study (EORTC 30001). Eur J Cancer 2006;42:1062–7.
[10] Van Poppel H, Goethuys H, Callewaert P, Vanuytsel L, Van de Voorde W, Baert L. Radical prostatectomy can provide a cure for well-selected clinical stage T3 prostate cancer. Eur Urol 2000;38:372–9.
[11] Hynynen Ouden D, Hop WC, Schröder FH. Progression in and survival of patients with locally advanced prostate cancer (T3) treated with radical prostatectomy as monotherapy. J Urol 1998;160:1392–7.
[12] Hsu CY, Joniau S, Oyen R, Roskams T, Van Poppel H. Outcome of surgery for clinical unilateral T3a prostate cancer: a single-institution experience. Eur Urol 2007;51:121–8, discussion 128–9.
[13] Gonttero P, Marchioro G, Picani R, et al. Is radical prostatectomy feasible in all cases of locally advanced non-bone metastatic prostate cancer? Results of a single-institution study. Eur Urol 2007;51:922–9, discussion 929–30.
[14] Berglund RK, Jones JS, Ulchaker JC, et al. Radical prostatectomy as primary treatment modality for locally advanced prostate cancer: a prospective analysis. Urology 2006;67:1253–6.
[15] Carver BS, Bianco FJ, Scardino PT, Eastham JA. Long-term outcome following radical prostatectomy in men with clinical stage T3 prostate cancer. J Urol 2006;176:564–8.
[16] Freedland SJ, Partin AW, Humphreys EB, Mangold LA, Walsh PC. Radical prostatectomy for clinical stage T3a cancer. Cancer 2007;109:1273–8.
[17] Martinez J, de la Riva S, Belón-López-Tomasey J, Marrero-Dominguez R, Alvarez Cruz E, Santamaría BP. Radical prostatectomy as monotherapy for locally advanced prostate cancer (T3a): 12 years follow-up. Arch Esp Urol 2004;57:679–92.
[18] Joniau S, Briganti A, Gonttero P, et al. Stratification of high-risk prostate cancer into prognostic categories: a European multi-institutional study. Eur Urol 2015;67:157–64.
[19] Stranne J, Brasso K, Brennhovd B, et al. SPGC-15: a prospective randomized study comparing primary radical prostatectomy and primary radiotherapy plus androgen deprivation therapy for locally advanced prostate cancer. Scand J Urol 2018;52:313–20.
[20] Jäderling F, Akre O, Aly M, et al. Preoperative staging using magnetic resonance imaging and risk of positive surgical margins after prostate-cancer surgery. Prostate Cancer Prostatic Dis 2019;22:391–8.
[21] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
[22] samverkanci. Rci. Nationellt vårdprogram prostatecancer: Regionalt cancercentrum. 2022. https://kunskapsbanken.cancercentrum.se/diagonoser/prostatecancer/vardprogram/.
[23] Steineck G, Bergmark K, Henningson L, al-Abany M, Dickman PW, Helgason A. Symptom documentation in cancer survivors as a basis for therapy modifications. Acta Oncol 2002;41:244–52.
[24] Billiet-Acceptation A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med 2014;370:392–42.
[25] Abdolah F, Karmes RJ, Suardi N, et al. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. J Clin Oncol 2014;32:3939–47.
[26] Kristiansen A, Dreven L, Delahunt B, et al. Prognostic significance and biopsy characteristics of prostate cancer with seminal vesicle invasion on radical prostatectomy: a nationwide population-based study. Pathology 2017;49:715–20.
[27] NHS. National Health Service Survey. Health survey for England, 2018: adult’s health data tables. https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england, 2018/health-survey-for-england-2018-data-tables.
[28] Folkhalsomyndighet/Publ Health Agency of Sweden. Folkhälsoenkäten (National Public Health Survey). Psykisk hälsa (själfrapporterat) efter årler, kön och år. 2020. http://bhm- app.folkhalsomyndigheten.se/Folkhalsodata/pIEWS/SV/B_HL/%E8/ _HLV__dPsykals/bv1psoyld px/.
[29] Authority SDH. Den Nationale Sundhedsprofil (National Health Survey). Sygelighed. Psykisk lidelse af mindre end 6 måneders varighed. 2017. https://www.danskernesundhed.dk/.
[30] Fransson P, Lund JA, Damber JE, et al. Quality of life in patients with locally advanced prostate cancer given endocrine treatment with or without radiotherapy: 4-year follow-up of SPCG-7/SFUO-3, an open-label, randomised, phase III trial. Lancet Oncol 2009;10:370–80.
[31] Sweden SCS. Hushåll (households). 2020. https://www.statistikdatabasen.scb.se/pxweb/sv/ssd/START__BE__BE0101__BE0101S/HushallT07/?loadedQueryId=105552&timeType=top&timeValue=1.

[32] Sweden SCS. Befolkningstatistik (population statistics). Personer efter hushållstyp, hushållsställning och kön 31 December 2020. https://www.scb.se/hitta-statistik/statistik-efter-amne/befolkning/befolkningens-sammansattning/befolkningstatistik/.

[33] Sweden SCS. Befolkningens utbildning (education level of the population). 2020. https://www.statistikdatabasen.scb.se/pxweb/sv/ssd/START__UF__UF0506/Utbildning/.

[34] Sweden SCS. Arbetskraftsundersökningarna (labor survey). 2020. https://www.statistikdatabasen.scb.se/pxweb/sv/ssd/START__AM__AM0401__AM0401A/NAKUBefolkning2Ar/?loadedQueryId=81625&timeType=from&timeValue=2001.

[35] Authority DSDH. Nationale Sundhetsprofil (National Health Survey Denmark). Overvægt og undervægt. Moderat eller svær overvægt. 2017. https://www.danskernessundhed.dk/.

[36] Sweden SCS. Body mass index. 2019. https://www.scb.se/hitta-statistik/temaomraden/jamstalldhet/jamstalld-halsa/bodymassindex/.

[37] Sweden FPHAo. Nationella Folkhälsoenkäten (National Health Survey). Levnadsvanor. Fysisk aktivitet (självrapporterat) efter ålder, kön och år. 2020. http://fohm-app.folkhalsomyndigheten.se/Folkhalsodata/pxweb/sv/B_HLV/B_HLV__aLevvanor__aadLevvanorfysak/hlv1fysaald.px/.

[38] Folkhalsomyndigheten/Public Health Agency of Sweden. Daglig tobaksrökning (daily smoking). 2021. https://www.folkhalsomyndigheten.se/folkhalsorapportering-statistik/tolkad-rapportering/folkhalsans-utveckling/resultat/levnadsvanor/tobaksrokning-daglig/.

[39] Authority SDH. Den Nationale Sundhetsprofil (National Health Survey). Rygning. Daglig rygning. 2017. https://www.danskernessundhed.dk/.

[40] Office for National Statistics. Annual population survey. Smoking habits in the UK and its constituent countries, 2019 edition of this dataset. 2019. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeproductivityandwellbeing/bulletins/smokinghabitsintheukanditsconstituentcountries/.