



<b>Sponsor/Sponsor-Investigator</b>	PD Dr. med. Volker Arndt
<b>Study Title:</b>	PROSTATE CANCER SURVIVORSHIP IN SWITZERLAND: A MULTICENTER POPULATION BASED RETROSPECTIVE COHORT STUDY
<b>Short Title/Study ID:</b>	PROCAS – Prostate Cancer Survivorship in Switzerland
<b>Protocol Version and Date:</b>	Version 1.1 / 13.07.2016
<b>Trial Registration:</b>	Nicht anwendbar
<b>Study Category with Rationale</b>	HFV Project - Category A, observational study linked with minimal risk. This research projects only involves a questionnaire based investigation of health related data and subsequent use of non-genetic personal health data, which is related only with minimal risks and stress for participants.
<b>Clinical Phase, see Basisformular:</b>	Nicht anwendbar
<b>Background and Rationale:</b>	<p>Prostate cancer (PC) is the most frequent diagnosed cancer in men in developed countries with age-adjusted incidence rates (ASRs) up to 184 per 100,000 in North-America (2013, world-standard).<sup>1-3</sup> However, not only incidence rates of prostate cancer are high. PC survivors account for the largest group of male cancer survivors on the world.<sup>4</sup></p> <p>In Switzerland, the age-adjusted incidence rate (ASR=159 per 100,000 persons per year; European-standard) is among the highest in Europe (European mean: ASR=106 per 100,000 persons per year; European-standard)<sup>5</sup> and it is projected that already 60,200 men (41% of all cancer cases in men) have a history of prostate cancer. This number increased since the year 2000 by more than 30,000 cases.<sup>6</sup> The number of projected long-term prostate cancer survivors (i.e. more than five years after diagnosis) even tripled since 2000 (2015: 32,818).<sup>7</sup> This rise is a result of a combined effect of demographic aging, improvements in therapy, and increased incidence due to wide-spread of PSA testing (in 2012 31% men in Switzerland – age 50 to 74 - reported that they did a PSA test in last 12 months).<sup>8</sup> Improvements in therapy and diagnostics have led to 5-years relative survival rates of prostate cancers of almost 90 % in Switzerland.<sup>9</sup></p> <p>In summary there are many men diagnosed with prostate cancer in Switzerland and their number will increase due to demographic aging. Although most men with PC nowadays survive the disease, they may experience disease- and/or treatment-related long-term effects on their physical, psychological, or social health.<sup>10</sup></p> <p><b>Health-Related Quality of Life</b></p> <p>Cancer is now considered as a chronic disease, which affects patients life over years and many survivors continue to experience negative effects of cancer and/or treatment on their daily lives well beyond the completion of therapy.<sup>11</sup> The life-altering burden of cancer has frame-shifted from a narrow focus on the direct effects of anti-cancer therapy and overall survival to a spectrum of medical and non-medical issues termed cancer survivorship.<sup>12</sup> An individual is considered to be a cancer survivor from the time of diagnosis and cancer survivorship is defined as process of living with, through, and beyond cancer.<sup>13</sup> Moreover, cancer survivorship encompasses quality of life aspects such as physical, psychosocial, and</p>

	<p>economic sequelae of cancer diagnosis and its treatment but it also includes issues related to health care delivery, access, and follow up care. Quality of life (QoL) has been defined as the difference, or the gap, between the hopes and expectations of the person and one's present life experience.<sup>14</sup> It is generally considered that QoL is best defined and measured from the individuals' perspective. QoL or even more specific and appropriate health-related quality of life (HRQoL) as a multidimensional concept, defines all aspects of survivors' well-being, as physical, psychological, social and spiritual well-being.<sup>10,15-20</sup></p> <p>According to the literature, overall QoL of long-term survivors of prostate cancer is comparable to age-matched controls.<sup>21,22</sup> However, issues of urinary, sexual, and bowel dysfunction remain problematic for prostate cancer survivors over the long term. Survivors report worse problems with urinary (e.g. leakage or incontinence) and sexual functioning (e.g., obtaining and maintaining erection) than controls. Although type of treatment appears to have no influence on overall HRQoL of life the severity of these specific problems varies according to primary treatment.<sup>16,20,23</sup></p> <p>This study wants to fill the gap in existing knowledge about health-related quality of life as well as disease and treatment related late effects of long-term survivors of prostate cancer in Switzerland. So far, the entire research regarding HRQoL and further survivorship issues in long-term survivors of cancer is relying on data mostly from the US and to a small proportion from Scandinavian countries, Netherlands, and the UK. Differences in health care administration including follow-up of cancer survivors and cancer rehabilitation may limit the generalizability of the current knowledge regarding quality of life in cancer survivors. Therefore, one of the primary objectives is to describe HRQoL in long-term prostate cancer survivors in Switzerland depending on personal and medical factors. Additionally, it will be tried to identify determinants and mechanisms for negative (as well as positive) effects on HRQoL in long-term prostate cancer survivors. This will help us to identify potentially modifiable factors amenable to intervention aiming to improve HRQoL in long-term prostate cancer survivors.</p>
<p><b>Objective(s):</b></p>	<p><b>Primary Project Objectives</b></p> <p>To describe long-term health-related quality of life of prostate cancer survivors in Switzerland depending on personal and medical factors:</p> <ul style="list-style-type: none"> <li>• What is the health-related quality of life among long-term prostate cancer survivors?</li> <li>• Does health-related quality of life of survivors differ between certain groups? (e.g. age; tumour stage; rural/urban; language group; socioeconomic status; comorbidities etc.)</li> <li>• What is the impact of the primary treatment (prostatectomy, radiotherapy, hormone therapy, watchful waiting and active surveillance, etc.) on health-related quality of life of prostate cancer survivors?</li> </ul> <p><b>Secondary Project Objectives</b></p> <p>2a. To identify determinants and mechanisms for negative (as well as positive) effects, such as pain, fatigue, mental health, comorbidities, resources, on health-related quality of life in long-term prostate cancer survivors.</p> <p>2b. To compare long-lasting physical effects (such as incontinence, memory problems, pain syndromes, osteoporosis, or fatigue) of prostate cancer survivors with respect to age, tumour stage, and treatment factors.</p>
<p><b>Outcome (if applicable, see Basisformular):</b></p>	<p><b>Primary Outcome</b></p> <ul style="list-style-type: none"> <li>• General and prostate cancer specific health related quality of life (EORTC QLQ-C30, QLQ-PR25, EPIC-26)</li> </ul>

<b>Primary Outcome Secondary Outcome</b>	<b>Secondary Outcomes</b> <ul style="list-style-type: none"> <li>• Fatigue: EORTC QLQ-FA13[12] (Remark: The new version of the EORTC QLQ-FA13 will be used. EORTC QLQ-FA12 expected to be published by spring/summer 2016)</li> <li>• Mental Health (MHI-5)</li> <li>• Spirituality: FACIT sp</li> <li>• Data about comorbidities</li> </ul>
<b>Study Design, see Basisformular:</b>	This is a Swiss multicentre population based retrospective cohort study with additional collection of current information about HRQoL, personal and medical data of long-term prostate cancer survivors using questionnaires and data of cancer registries.
<b>Inclusion/Exclusion Criteria, see Basisformular:</b>	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> <li>• Male subjects</li> <li>• Diagnosed with prostate cancer (ICD-10 C61) between 1th January 2006 and 31th December 2010</li> <li>• Registered by one of the following cancer registries: BS/BL, FR, GR/GL, SG/AR/AI, VS &amp; ZH</li> <li>• Age at diagnosis between 25 and 75 years</li> <li>• Alive at time of enrolment</li> <li>• Able to complete the questionnaire (assistance is possible)</li> <li>• Able to understand German, French or Italian</li> <li>• Written informed consent</li> </ul> <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> <li>• Death</li> <li>• Not able to complete the questionnaire</li> </ul>
<b>Measurements and Procedures:</b>	<p>Study participants will receive once a questionnaire which includes the following international validated instruments:</p> <p>General and prostate cancer specific health related quality of life (EORTC QLQ-C30, QLQ-PR25, EPIC-26)  Fatigue: EORTC QLQ-FA13 (Remark: new version EORTC QLQ-FA12 will be used, EORTC QLQ-FA12 expected to be published by end of 2015)  Mental Health (MHI-5)  Spirituality: FACIT sp</p> <p>Additionally, referring physicians are asked to answer eight questions about the patients' prostate cancer stage, secondary cancer, treatment details and recurrence of prostate cancer.</p>
<b>Study Product/Intervention according to KlinV, if applicable:</b>	Not applicable
<b>Comparator(s) (if applicable):</b>	Not applicable
<b>Number of Participants with Rationale (if no Power Analysis conducted):</b>	A total of 1400 patients will be approached in order to be enrolled in the project. Assuming a drop-out rate of 50%, based on previous pertinent studies of the PI, and the impracticality to send reminders we expect to recruit 700-800 participants.
<b>Study Duration:</b>	20 months
<b>Study Schedule:</b>	Enrolment of participants between 11/2016 – 06/2017

<p><b>Person involved in the research project:</b></p>	<p>Salome Adam, MSc  Coordinating Investigator  Epidemiology, Biostatistics and Prevention Institute  University of Zurich  Hirschengraben 84  CH-8001 Zürich  Email: salome.adam@uzh.ch  Phone: +41 44 634 53 79  Fax: +41 44 634 54 44</p> <p>Dr. Matthias Lorez  Senior Biostatistician  National Institute for Cancer Epidemiology and Registration  Seilergraben 49  CH-8001 Zürich,  Email: ml@nicer.org  Phone: +41 44 634 46 45  Fax: +41 44 634 54 4</p> <p>Dipl.-Psych Anita Feller, MSc  Epidemiologist  NICER  c/o Universität Zürich  Seilergraben 49  CH-8001 Zurich  Email: anita.feller@nicer.org  Phone: +41 44 634 59 35</p> <p>Nina Pupikofer  Administration  NICER  c/o Universität Zürich  Seilergraben 49  CH-8001 Zurich  Email: nina.pupikofer@nicer.org  Phone: +41 44 634 53 74</p> <p>Regina Nanieva  Medical Information Specialist  c/o Universität Zürich  Seilergraben 49  CH-8001 Zurich  Email: regina.nanieva@nicer.org  Phone: +41 44 634 53 74</p> <p>Student assistants and cancer registries assistants to be hired</p>
<p><b>Study Centre(s):</b></p>	<p>Krebsregister beider Basel  Dr. med. S. Mohsen Mousavi  Gesundheitsdepartment des Kantons Basel-Stadt, Medizinische Dienste  Bewilligungen und Support  Gerbergasse 13  CH-4001 Basel  Email: mohsen.mousavi@bs.ch  Phone: +41 61 267 49 23  Fax: +41 61 267 49 21</p>

	<p>Registre fribourgeois des tumeurs  Dr. med. Bertrand Comey  St-Nicolas-de-Flüe 2, CP 96  CH-1705 Fribourg  Email: comey@liguessante-fr.ch  Phone: +41 26 425 54 05  Fax: +41 26 424 54 01</p> <p>Krebsregister St. Gallen–Appenzell  MPH, Dr. med. Harald Frick  Krebsliga St. Gallen-Appenzell  Flurhofstr. 7  CH-9000 St. Gallen  Email: Harald.Frick@kssg.ch  Phone: +41 71 494 21 17  Fax: +41 71 494 61 76</p> <p>Krebsregister Graubünden und Glarus  Dr. med. Harald Frick  Kantonsspital Graubünden  Institut für Pathologie und Rechtsmedizin  Loestrasse 170  CH-7000 Chur  Email: silvia.ess@kssg.ch,  Harald.Frick@kssg.ch  Phone: +41 81 256 65 56  Fax: +41 81 256 65 44</p> <p>Registre Valaisan des Tumeurs  Dr. med. Isabelle Konzelmann  Observatoire valaisan de la santé  Avenue Grand-Champsec 86  CH-1950 Sion  Email: isabelle.konzelmann@ovs.ch  Phone: +41 27 603 48 55  Fax: +41 27 603 49 74</p> <p>Krebsregister Zürich und Zug  PD Dr. oec. troph. Sabine Rohrmann, MPH Universitätsspital Zürich  Vogelsangstr. 10  CH-8091 Zürich  Email: sabine.rohrmann@usz.ch  Phone: +41 44 255 56 36  Fax: +41 44 255 56 36</p>
<b>Statistical Analysis incl. Power Analysis</b>	<p>Descriptive, univariate and multivariate statistics.  Comparison of mean values, correlations and regression analysis.  E.g. The association between primary treatment(s) received and mean (a) global HRQoL, (b) functional and (c) symptom scores will be assessed by multivariate linear regression while controlling for potential confounding factors.</p>
<b>GCP Statement:</b>	<p>This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.</p>

**Explanation for the Inclusion of vulnerable Subjects (if applicable):**

No vulnerable subjects are included in the study.

---

**Recruitment Procedure (if applicable : Advice/Flyer have to be submitted ; if applicable, please indicate the Localisation / Medium (which Newspaper)**

The study is based on a pooled analysis of retrospectively constructed cohorts of long-term prostate cancer survivors (men, diagnosis between January 2006 and December 2010, age between 25 and 75 years at diagnosis). A postal data collection is supposed to assess HRQoL 5-10 years after their prostate cancer diagnosis.

Potential participants will be identified via the cancer registries BS/BL, FR, GR/GL, SG/AR/AI, VS & ZH.

In principle, potential participants will be identified by participating cancer registries, whereas information of survivors and obtaining informed consent will be accomplished by the referring urologist. Participants will receive once a questionnaire. In case of missing information participants will be once recontacted.

**Study Procedure/Flowchart with Timelines: Study specific Examinations have to be clearly identified**

	2016						2017												2018	
	07	08	09	10	11	12	01	02	03	04	05	06	07	08	09	10	11	12		
<b>Construction of cohort including vital status review</b>																				
<b>Data Collection</b>					FP FV								LP LV							
<b>Getting confirmation of urologists in the study region that they want to participate in the study</b>																				
<b>First recruitment phase</b>																				
Informing patients' referring physicians																				
Mailing Questionnaires to patients																				
Monitoring of feedback (including checking completeness of questionnaires and informed consent)																				
Informing patients' referring physicians that his patients participated and asking for patients' medical information																				
<b>Potential second recruitment phase</b>																				
Informing patients' referring Physicians																				
Mailing Questionnaires to patients																				
Informing patients' referring Physicians that his patients' participated and asking for patients' medical information																				
Monitoring of feedback																				
<b>Data Entry and Validation</b>																				
<b>Data Analysis &amp; Preparation of Publications</b>																				

---

**Risks/ Inconveniences, which are Study specific:**

Through the questionnaire it is possible that participants and their relatives/friends can have bad memories about their diagnosis/therapy or a flashback. Moreover, they maybe start to question their health status again what can cause stress.

---

**Coverage of Damages: Insurance: no**

Category A project, no insurance needed

---

**Ethical Considerations:**

1. Please describe the potential gain of new knowledge obtained with this study, and its meaning for patients/society.

The results of the envisioned project will help (a) to create a better knowledge regarding adverse diagnosis and treatment-related outcomes after prostate cancer such as late effects of treatment and poor quality of life; (b) to develop strategies to prevent and to control these adverse cancer diagnosis and treatment-related outcomes; and (c) to optimize health after prostate cancer treatment including better follow-up care and surveillance of cancer in the long run.

2. Please give an assessment of the benefit/risk relationship for the patient.

Participation in the study is only linked with very small psychological risks (e.g. flashback of bad memories). Moreover, participants will not have a direct benefit from participating in the study.

However, it might be that participants and/or their referring physicians become attentive on potential impacts of the prostate cancer diagnosis and the following therapies. These impacts can be addressed later-on. So this study can increase the sensitivity on health problems related with prostate cancer diagnosis and prostate cancer treatments.

3. Please explain, why the methodology is also ethically appropriate to gain new generalizable knowledge (for ex. double-blind, placebo, sham, vulnerable subjects, emergency cases, partial information only etc.)

The population based approach of this project allows gathering new generalizability knowledge. So far, no data about HRQoL of long-term prostate cancer survivors is available in Switzerland. Moreover, patients are the most important data source for HRQoL assessment.



---

### The most relevant References:

1. American Cancer Society; 2015 1–57 (2015 American Cancer Society. Global Cancer Facts & Figures. 3. Edition, Atlanta).
2. Siegel, R. *et al.* Cancer Treatment and Survivorship Statistics , 2012. *CA. Cancer J. Clin.* **62**, 220–241 (2012).
3. Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, M. Cancer Statistics Review, 1975-2012 - SEER Statistics. *SEER data Submiss.* (2014).
4. Parkin, D. M., Bray, F., Ferlay, J. & Pisani, P. Global cancer statistics, 2002. *CA. Cancer J. Clin.* **55**, 74–108
5. EUCAN Factsheets | Prostate cancer. EUCAN at <<http://eco.iarc.fr/EUCAN/CancerOne.aspx?Cancer=29&Gender=1>> Last visit: 1.11.2015
6. NICER Nationales Institut für Krebs epidemiologie und -registrierung Schweiz. (2010). at <<http://www.nicer.org/NicerReportFiles2015/DE/report/atlas.html?&geog=0>> Last visit: 1.11.2015.
7. Lorez, M., Heusser, R. & Arndt, V. Prevalence of Cancer Survivors in Switzerland. *Schweizer Krebsbulletin* 285 – 288 (2014).
8. Ulrich Wagner, M. D. *Gesundheitsstatistik 2014.* (Bundesamt für Statistik (BFS), 2014).
9. Dehler, S., Rohrmann, S. & Lorez, M. Trends in Prostate Cancer Survival in Switzerland. *Schweizer Krebsbulletin* **1**, 54–58 (2013).
10. Galbraith, M. E., Arechiga, A., Ramirez, J. & Pedro, L. W. Prostate Cancer Survivors' and Partners' Self-Reports of Health-Related Quality of Life, Treatment Symptoms, and Marital Satisfaction 2.5-5.5 Years After Treatment | ONF. *Oncol Nurs Forum* **32**, E30–41 (2005).
11. Gotay, C. C. & Muraoka, M. Y. Quality of life in long-term survivors of adult-onset cancers. *J. Natl. Cancer Inst.* **90**, 656–67 (1998).
12. Office of Cancer Survivorship. at <<http://cancercontrol.cancer.gov/ocs/>> Last visit: 26.10.2015.
13. The NCCS Definition of a 'Cancer Survivor'. at <<http://www.canceradvocacy.org/news/defining-cancer-survivorship/>> Last visit: 08.09.2015
14. Ferrell BR, H. D. K. Quality of Life Among Long-Term Cancer Survivors | Cancer Network. *Oncology* **11**, 565–571 (1997).
15. Ferrell, B. R., Grant, M. M., Funk, B., Otis-Green, S. & Garcia, N. Quality of life in breast cancer survivors as identified by focus groups. *Psychooncology*. **6**, 13–23 (1997).
16. Korfage, I. J. *et al.* Five-year follow-up of health-related quality of life after primary treatment of localized prostate cancer. *Int. J. Cancer* **116**, 291–6 (2005).
17. Mols, F. *et al.* Does diabetes mellitus as a comorbid condition affect the health-related quality of life in prostate cancer survivors? Results of a population-based observational study. *BJU Int.* **102**, 1594–1600 (2008).
18. Dalkin, B. L., Wessels, H. & CUI, H. A National Survey Of Urinary And Health Related Quality Of Life Outcomes In Men With An Artificial Urinary Sphincter For Post-Radical Prostatectomy Incontinence. *J. Urol.* **169**, 237–239 (2003).
19. Van Lin, E. *et al.* Long-term outcome and morbidity after treatment with moderate hypofractionated radiotherapy, gold markers and endorectal balloon for prostate cancer. in *Strahlentherapie und Onkol.* **187**, 45 (2011).
20. Penson, D. F. *et al.* 5-year urinary and sexual outcomes after radical prostatectomy: results from the prostate cancer outcomes study. *J. Urol.* **173**, 1701–1705 (2005).
21. Galbraith, M. E., Arechiga, A., Ramirez, J. & Pedro, L. W. Prostate cancer survivors' and partners' self-reports of health-related quality of life, treatment symptoms, and marital satisfaction 2.5-5.5 years after treatment. *Oncol. Nurs. Forum* **32**, E30–41 (2005).
22. Joly, F. *et al.* Health-related quality of life and sequelae in patients treated with brachytherapy and external beam irradiation for localized prostate cancer. *Ann. Oncol.* **9**, 751–7 (1998).
23. Miller, D. C. *et al.* Long-term outcomes among localized prostate cancer survivors: HRQOL changes 4 to 8 years following brachytherapy, external radiation and radical prostatectomy. in *J. Urol.* **171**, 312–313 (2004).