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Dose intensified radiotherapy in patients with prostate cancer and PSA progression after prostatectomy (Study SAKK 09/10)

Information on the results of the trial

We report below on the key results of the study entitled "Dose intensified radiotherapy in patients with prostate cancer and PSA progression after prostatectomy".

Trials are very important in enabling progress to be made in medicine and science. You can make a significant contribution here by agreeing to be treated in the context of a clinical trial, and thereby help future patients in terms of answering their health-related questions and developing new treatments for them or improving existing treatments. The Swiss Group for Clinical Cancer Research (SAKK) would like to express its sincere thanks to you for your participation and commitment.

1. Name of the trial

The full German name of the trial:

Dosisintensivierte Salvage-Strahlentherapie bei biochemisch rezidiviertem Prostatakrebs ohne makroskopische Erkrankung. Eine randomisierte Phase-III-Studie
(Original English title: Dose intensified salvage radiotherapy in biochemically relapsed prostate cancer without macroscopic disease. A randomized phase III trial)

Explanation of terms:

- *"Dose intensified radiotherapy"* means that the tumor is exposed to a dose of radiation that is higher than normal.
- *"PSA progression":* Prostate-specific antigen (PSA) is a substance produced in the prostate. In men with prostate cancer, the PSA level in the blood is often elevated. After prostatectomy, the PSA level drops. If the PSA level is seen to rise again in the follow-up tests, this indicates that the cancer has relapsed.
- *"randomized":* In the study, the participants received either a lower or higher dose of radiation (two treatment groups). The patients were randomly assigned to one of the two groups (randomized).
- *"Phase III trial":* The efficacy and tolerability of the treatment were investigated in a large number of patients.

Further explanations of technical terms can be found in the glossary at the end of this document.

2. Organization of the trial

The Swiss Group for Clinical Cancer Research (SAKK) has planned and implemented this trial.

For more information about SAKK visit the website: www.sakk.ch.

3. General information about the trial

Prostate-specific antigen (PSA) is a substance produced in the prostate. In men with prostate cancer, the PSA level in the blood is often elevated. After the cancer is removed, the PSA level drops. If the PSA is seen to rise again in the follow-up tests after the prostatectomy, this indicates that cancer cells are again present in the body (tumor relapse). Such a relapse can even occur years after the prostatectomy. If the tumor cells are found only at the site of the previous episode of prostate cancer (local relapse), the treatment is irradiation of this site (radiotherapy).
The dosage of radiotherapy in such a situation differs from hospital to hospital (from 64 to 70 grays). However, it is still not clear whether a higher dose of radiation is more effective than a lower one. A higher radiation dose also usually causes more side effects than a lower dose. It is not yet known whether these side effects might be so harmful to the patient that a higher radiation dose is not beneficial. These unresolved questions were investigated in study SAKK 09/10.
Men whose PSA level rose again after a prostatectomy for prostate cancer and who experienced a local tumor relapse (no metastases in the lymph nodes or other organs) participated in the study.

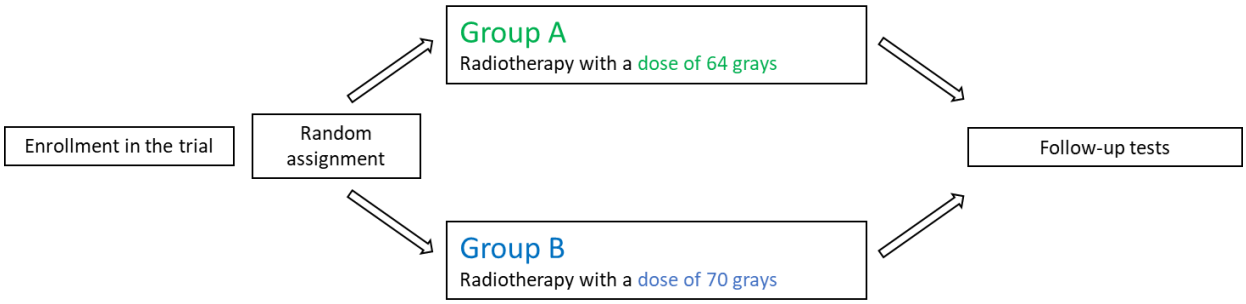
4. Participants

350 patients were enrolled in the study between February 2011 and April 2014. The data for 344 patients were evaluated in the most recent analysis. The PSA level had progressed in all participants after the prostatectomy. Various investigations had indicated that this PSA progression was not attributable to the formation of metastases, but was rather a local relapse of the prostate cancer. The participants were treated in Switzerland (14 hospitals), Germany (11 hospitals) and Belgium (3 hospitals).

5. Course of the trial and trial treatment

All trial participants were randomly assigned to one of two treatment groups:
The 170 participants in group A received radiotherapy with a total dose of 64 grays (several radiotherapy sessions over 6.4 weeks).
The 174 participants in group B received radiotherapy with a total dose of 70 grays (several radiotherapy sessions over 7 weeks).

Regular follow-up tests were carried out after the end of the treatment. These tests were scheduled for 3, 6 and 12 months in the first year after the radiotherapy, and then every 6 months over the next two years, and subsequently once a year for up to about ten years after completion of the radiotherapy.



6. Investigated factors

Various factors were investigated in connection with the trial, including:

- *Time to PSA progression:* In how many participants, and after what period after the start of treatment, did a further rise in the PSA level occur?
- *Safety and tolerability of the treatment:* What are the side effects of the radiotherapy? How severe are the side effects?
- *Quality of life:* What is the quality of life of the trial participants like during and after the treatment?

7. Results of the trial

Time to PSA progression:
7 years after the inclusion of the last patient, the median time to PSA progression in the group receiving the lower dose was 8.2 years, compared to 7.6 years in the group receiving the higher dose. The percentage of patients with **no** PSA progression six years after the start of the radiotherapy was 62% in the group receiving the lower radiation dose and 61% in the group receiving the higher radiation dose.

Safety and tolerability of the treatment:
Significant, but not serious, side effects in the urinary tract (e.g. frequent urge to urinate) were experienced by 48 patients (29%) in the group receiving the lower radiation dose and in 51 pa-

tients (30%) in the group receiving the higher radiation dose.
Significant, but not serious, side effects in the gastrointestinal tract (e.g. diarrhea) were experienced by 19 patients (11.5%) in the group receiving the lower radiation dose and in 39 patients (22%) in the group receiving the higher radiation dose.
Erectile dysfunction occurred in almost a third of the patients in both treatment groups.

Quality of life:
The quality of life of the participants was recorded by means of questionnaires during and after the treatment. The participants were asked about their quality of life in various areas, for example physical and mental performance, emotional stress, social life and sexuality. They were also asked about the stress associated with various symptoms, for example fatigue, pain, insomnia, gastrointestinal disorders, problems with urination, incontinence, etc.
At the start of the study, the quality of life of many participants was impaired particularly as a result of emotional stress, problems with urination, incontinence, sexual problems and general stress. The symptoms during urination or associated with incontinence deteriorated in the first three years after the start of the study, to a greater extent in the group receiving the higher radiation dose than in the group receiving the lower radiation dose. After five years, however, this difference between the groups was no longer apparent. No differences between the groups were observed in the other areas of quality of life.

8. Significance of the trial results

Study SAKK 09/10 delivered three key findings:

- The higher total dose did not result in a longer period without PSA progression.
- Gastrointestinal side effects occurred more frequently after a higher total dose than after radiotherapy with a lower dose.
- The stress caused to patients by symptoms and an impaired quality of life was identical in both treatment groups.

Consequently, the radiotherapy with a higher dosage does not provide patients with any additional benefit, but does increase the risk of side effects.
In future, patients with PSA progression after prostatectomy should preferably be treated with a total dose of 64 grays instead of 70 grays. However, the researchers who conducted the study point out that the decision concerning the best treatment must continue to be made on a case-by-case basis for every patient.

Annex: Glossary

- **Gray:** Unit for the energy dose of radiation. The radiation dose during radiotherapy is expressed in grays.
- **Incontinence:** Inability to retain urine in the bladder.
- **Local:** here: only at that part of the body where the prostate is located, not at other body sites.
- **Median:** In a set of data, the median is in the middle: half of the numbers are below and half above the median.
- **Metastasis:** Secondaries of malignant tumors in the lymph nodes or in a more remote organ.
- **Phase III trial:** Trial in which the safety and efficacy of a treatment is investigated in a large number of patients.
- **PSA:** Abbreviation for "prostate-specific antigen", a substance formed in the prostate.
- **Radiotherapy:** Treatment involving the use of ionizing radiation.
- **Recurrence:** Renewed occurrence of a disease.
- **Tumor recurrence:** Recurrence of a cancer after a successful treatment.
- **Single-arm trial:** Trial in which all participants receive the same treatment.
- **Open-label trial:** Trial in which the researchers and the participants know what treatment is being used.
- **Phase I trial:** Trial in which an active substance that has never been previously tested in humans is administered to a small number of cancer patients with the aim of finding a safe dose.
- **Phase II trial:** Trial in which the efficacy of a treatment is investigated in a fairly large number of patients.