# Should we affraid of induced cancer in group of patients after radical radiotherapy of prostate cancer?

**Piotr MILECKI, Anna ADAMSKA, Andrzej ROSZAK, Dominika KALETA**

**Received:** 4.06.2009
**Accepted:** 3.11.2009
**Subject:** rewiev article

Greater Poland Cancer Centre

**Address for correspondence:**
Mr Piotr Milecki
Greater Poland Cancer Centre
Garbary 15 Str
61-866 Poznań, Poland
e-mail: piotr.mielcki@wco.pl

ABSTRACT

Radiotherapy is one of the basic methods of radical treatment of prostate cancer. Because of that getting to know all factors of post-radiation complications, and in consequence the possibility to limit them, is one of the challenges of contemporary radiotherapy.
One of the potential complications associated with radiation treatment is radiation-induced cancer. Despite a whole range of epidemiological analyses there is still lacking a fully credible model that would allow one to estimate the magnitude of risk of inducing such cancers. The last decades have seen the entry into clinical practice of technologically advanced methods of radiation therapy, such as the 3DCRT and IMRT. As the previous epidemiological analyses refer mainly to older radiation techniques, there is still a lack of credible data estimating the risk of inducing secondary cancers for new techniques, and in particular IMRT. It should be emphasized that IMRT allows one to escalate the dose, which may contribute to the improvement of radiotherapy effectiveness. From this there follows a new problem to be solved in future, i.e. how the escalation of the dose may influence the magnitude of risk of radiation carcinogenesis.
The problem of carcinogenesis may concern the group of younger patients for whom long survival is very likely, and the competitive edge of RT relative to surgery, in particular in the aspect of late complications, has to be thoroughly justified.

**KEY WORDS:** prostate cancer, radiotherapy

## INTRODUCTION

Radiotherapy alongside radical prostatectomy is among the basic methods of radical treatment of prostate cancer [1, 2, 3]. The increase in incidence of prostate cancer in the last decades has resulted in it becoming one of the most frequent malignant cancers among men [4] in the developed countries. It should also be emphasized that the increase of radiotherapy effectiveness translates into prolongation of survival of treated patients. Because of that, getting to know all factors affecting occurrence of potential side-effects of the treatment and at the same time actions aimed at their maximum limitation are among the challenges of contemporary radiotherapy. One such complication may be cancer induction by radiation. The belief is common that ionizing radiation is a carcinogenic factor. An essential source of information about the influence of ionizing radiation on carcinogenesis was the observations of individuals who experienced exposure to ionizing radiation after the atom bomb explosion in Hiroshima [5].

A second group of observations concerns patients undergoing medical procedures using ionizing radiation [6]. It was determined on the basis of previously gathered data that the time between exposure of healthy tissues and the development of cancer is for solid tumours over 10 years, and for leukaemias and lymphomas this time is shorter – 5 years [7]. Moreover, these observations permitted a hypothesis to be formulated stating that the relation between administered dose and the risk of cancer induction by radiation exhibits linear dependence within a dose from 1 to 2.5 Sv. The carcinogenesis model (linear no-threshold (LNT) model) thus established is still valid despite a whole range of doubts associated with its credibility. Among other things, this model does not make possible a reliable assessment of the risk of a carcino-

genic effect in the case of exposure of healthy tissues outside the range of doses between 1 Gy and 3 Gy. In the accepted LNT model assessment of the risk of a carcinogenic effect in the case of exposure of healthy tissues to low doses, below 1 Gy, cannot be made, because the approximate risk of cancer induction was derived only by extrapolating the effect from the range of higher doses. The effect of higher doses of ionizing radiation used principally in radiotherapy, i.e. doses exceeding 3 Gy, has still not been explained. Generally there are two approaches to this problem. In the first of them a decline of risk of carcinogenesis, caused by increased death of mutated cells that are a potential source of carcinogenesis, is suggested. On the other hand, in the second approach the possibility of a plateau effect is assumed. In consequence the risk of cancer induction by radiation may not depend in a directly proportional way on the level of the administered dose. However, theoretical deliberations themselves, or even in vitro research, still do not permit a real assessment of this problem. Moreover, it was assumed in the linear model that there is not a threshold dose below which ionizing radiation is safe. Such an approach may be at odds among other things with a different hypothesis, radiation hormesis, in which it is assumed that low doses of ionizing radiation have simply a favourable effect on a cell [8].

Previous attempts to estimate the influence of RT on the risk of induction of a malignant tumour in clinical practice have encountered a whole range of methodological difficulties [9, 10]. In the first place there was the impossibility of unequivocal classification of a tumour as an induced tumour.

This results primarily from the fact that the diagnosed cancer does not have characteristic morphological and/or histological features typical only for cancer induced by radiotherapy. In consequence of this there also follow further methodological problems. The only way to determine to what extent RT is responsible for an increase in the number of induced malignant tumours is a study comparing the incidence of second cancers in a group of patients who underwent RT with a group of patients who underwent another kind of treatment. Patients after radical prostatectomy are taken as the control group. One of the main faults of these kinds of analyses is the lack of full knowledge of the essential factors responsible for inducing cancer, which means that we do not have knowledge of their influence on the carcinogenetic process.

Ranking foremost among these factors are genetic predispositions, environmental factors (professional exposure, medicinal drugs, viral diseases, hormonal profile of patient) and addictions, e.g. smoking [11]. It should be emphasized that ionizing radiation is only one of numerous factors responsible for carcinogenesis. Despite the limitations mentioned above, epidemiological analysis is still the most valuable source of knowledge about radiotherapy as a carcinogenic factor in patients with prostate cancer.

## Factors that may increase the risk of cancer induction by radiotherapy

### New techniques of irradiation

The introduction of technologically advanced radiotherapy in the last decades has led some researchers to conjecture that such therapy might be associated with a greater risk of inducing cancer than in a two-dimensional technique. This hypothesis is grounded in the fact that it is precisely within doses between 1 Gy and 4 Gy that the greatest risk of cancer induction by radiation can be expected. Transition from the conventional 2D radiotherapy to 3D conformal radiotherapy enabled reduction of the volume of healthy tissues receiving high doses of radiation, and on the other hand led to the possibility to administer a higher dose to a tumour together with parallel limitation of the dose to healthy tissues adjacent to the tumour [12]. Because of the above the modern techniques of radiotherapy may lead to a drop in the number of sarcomas that develop within the volume of tissues exposed to high doses of radiation [13, 14]. Also, although less certain, a small fall in the number of cancers within areas adjacent to the tumour can be expected.

On the other hand, in the conformal technique, and in particular IMRT, it is necessary to apply a greater number of therapeutic beams, which is associated (as shown by the histograms) with the deposition of low doses,

much smaller than 2 Gy, in a greater volume of healthy tissue.

Additionally, in this technique there is an increase in monitor units by a factor of 2 to 3, which consequently increases the exposure of the whole body to ionizing radiation. Additional exposure of the patient may result from increased leakage of radiation through the accelerator head. Both these facts have important consequences for the risk of radiation-induced cancer. According to theoretical assumptions, IMRT may increase the risk of development of secondary cancers almost twofold in comparison with conventional conformal radiotherapy, i.e. from 1% to 1.75% for patients surviving over 10 years, and this level may potentially increase in the case of longer survival (in younger patients) [13]. Taking into account that sarcomas appear only within healthy tissues subjected to irradiation with a high dose, it does not seem that between IMRT and 3D there was a significant difference in respect of inducing these tumours. However, in the case of using IMRT an increase in the number of cancers, in particular outside the close surroundings of the tumour, can be expected.

The next factor that may in future increase the risk of cancer induction by radiation is the improvement of therapy effectiveness that would translate to prolongation of the time of survival of patients beyond the typical latency period of carcinogenesis. In the developed countries, in the last two decades, a significant improvement of survival of patients with prostate cancer has been noted, to which the improvement of radiotherapy effectiveness might have contributed [15]. An additional factor associated with modern radiotherapy techniques that may increase the risk of radiation-induced cancer is the use of additional doses of radiation in the process of verification of the irradiation treatment [16]. The dose administered through critical organs during a single computed tomography examination in a patient during the planning of radiotherapy varies between 1 mGy and 40 mGy depending on the volume anticipated for irradiation and technical parameters of the apparatus [17]. The next source of additional radiation dosage, which is from 10 mGy to 20 mGy, is the imaging process verifying geometric correctness of irradiation, and it should be emphasized that during the whole course of irradiation it is performed many times [18]. In general, the more complicated the plan of irradiation treatment, the higher the dose of ionizing radiation that will be deposited outside the target volume. It still remains an unsolved issue how the above doses may influence the risk of inducing cancer in the context of the whole irradiation process. Exposure to additional radiation will probably increase together with the progress in irradiation techniques and diagnostics applied in the planning process of radiotherapy, e.g. positron emission tomography [19]. In that case, should all these doses be registered, considering also doses from the diagnostic process? A clinician has the obligation to assess and optimise all exposures to radiation in every situation. However, in clinical practice this is extremely difficult, and basically unfeasible. Therefore we should aspire more to develop generally applicable rules of practice, remembering that the more complicated the treatment, the higher the additional dose of ionizing radiation the patient will receive.

## The most important epidemiological research assessing the risk of second cancer related to radiotherapy

According to Harrison et al. [20] the risk of radiation-induced cancer in the case of treatment with irradiation of prostate cancer up to the dose of 74 Gy is between 2.2 and 8.2 per 10 000 patients a year. Movsas et al. [21] made an analysis of the risk of inducing cancer, based on observation data of 18 135 patients registered in the Connecticut Tumor Registry and 543 patients from Fox Chase Cancer Center. The authors compared the number of secondary malignant cancers diagnosed in the group of 18 135 patients with prostate cancer after surgery with the number of identical cancers noted in the group of 543 patients in which RT was applied.

In the group that was not subjected to radiotherapy in 1053 (5.8%) patients a secondary primary cancer was noted, and in the group of patients who underwent radiotherapy a secondary primary cancer was noted in 31 (5.7%) patients. A fact worth noting is that among these 31 patients in whom cancer occurred, as

many as 82% had a medical history of smoking and/or drinking alcohol. The research shows that although the risk of development of cancer after previous treatment of prostate cancer increases with time, it is not typically different in any period of time between the above-mentioned groups of patients. Only the number of melanomas revealed in the group of patients subjected to radiotherapy was significantly higher in comparison with the quantity expected for a comparable age group ($p<0.001$). It should be noted in summary that 5 out of 31 cancers (16%) appeared in the irradiated field (4 bladder cancers and 1 rectum cancer), 4 of these within the first 3 years from the treatment and 1 not until 9 years after radiotherapy. The other 84% of cancers developed outside the irradiated area. The authors emphasize that for the period up to 10 years after irradiation there is not an increased risk of cancer development. It is essential that this risk is not higher in younger patients with the disease localized to the prostate (< pT2c), patients who usually have a choice between surgical treatment and radiotherapy. In the study by Neugut et al. [22] 141 761 patients with diagnosed prostate cancer were subjected to analysis. In this group RT was applied in 34 889 (24.6%) patients, and in the other 106 872 (75.4%) surgical treatment was performed.

The authors, within the eight-year observation period, found in patients treated by irradiation a significant increase in incidence of malignant bladder cancers (RR=1.5, 95% CI [1.1–1.2]).

Brenner et al. [23] carried out an analysis of incidence of secondary cancers in two groups of patients, i.e. surgically treated or RT treated. In the group of 70 539 patients in whom only surgical treatment was performed the authors observed 5055 cases of secondary cancers.

Meanwhile in the second group, comprising 51 584 patients, in whom only RT was applied, 3549 cases of secondary cancers were noted. In the above study stratification of patients was done with reference to time of cancer becoming apparent, age and cancer location. The authors state in the summary that RT involves a 6% increase of the risk of occurrence of solid tumours ($p=0.02$), and together with the prolongation of the time of observation to 5 and 10 years this risk increases respectively to 15% and 34%. Organs in which an increase in the number of registered cancers was noted were (in order) bladder, rectum and lungs. Moreover, an increased incidence of sarcomas was observed only in those healthy tissues which received a high dose. The authors did not note increased incidence of leukaemia. Noteworthy is the observed increase in incidence of lung cancers, and it should be emphasized that the authors excluded the difference in intensity of the habit of smoking between the analyzed groups of patients. It was stated in summary that the general risk of occurrence of induced cancer in patients treated with radiation was 1/290, and in patients who survived over 10 years after the completion of RT this risk increased to 1/70. The analysis carried out by Pickles et al. [24] was based on data from the register of cases in the period 1984 to 2000, during which generally 39 261 cases of prostate cancer were noted. Among this group in 9890 RT was applied. Comparison of the numbers of secondary cancers in the irradiated group with those surgically treated shows that a significant increase of risk of cancer after RT was noted only with respect to colorectal cancer (RR=1.21, $p=0.03$) and sarcomas (RR=2.49, $p=0.016$). It is worth noting the observed increase of risk of the occurrence of secondary cancers in younger patients (1/70) in comparison with patients of more advanced age (1/220). The above differences may result from the fact that RT in younger patients, due to their longer time of survival, paradoxically creates a greater risk of induced cancer becoming apparent.

The authors state that RT causes a small increase in incidence of secondary cancers that is only 6% (not reaching the level of statistical significance).

Wayne et al. [25] did the first assessment of the influence of irradiation on the risk of inducing rectal cancer. Among 33 831 irradiated patients with prostate cancer 243 (0.7%) were noted with rectal cancer. In comparison, in the group of 167 607 patients surgically treated this cancer was found in 578 (0.3%), and in the group of 36 335 persons who were neither operated on nor irradiated it was found in 227 (0.8%) persons. The statistical analysis revealed that the age difference between the

researched groups was the most significant parameter influencing the differences in the noted numbers of rectal cancers. After consideration of the mentioned age difference, the authors did not find any more significant increase in risk of occurrence of rectal cancer in patients who underwent irradiation.

Moon [26] et al. studied the size and significance of the observed relation between cases of secondary cancer after 5 years from RT in the population of men with prostate cancer who were in the SEER database. Patients treated with RT had a statistically higher risk of developing secondary cancer in areas potentially connected with irradiation, including the bladder (HR: 1.63) and rectum (HR: 1.60). Patients after RT had moreover higher risk of cancer development in upper parts of the body which were not connected with exposure to higher doses of radiation: caecum (1.63), transverse colon (1.85), brain (1.83), stomach (1.38), melanoma (1.29), lung and bronchi (1.25). As the authors point out, RT is still connected with the risk of occurrence of secondary cancers, including leukaemias, sarcomas, thyroid, lung and bladder cancers. The next important conclusion resulting from this study is that the latency period between exposure and cancer appearance exceeds 5 years, and on average is 15 years. Secondary cancers may appear in the radiation field, but cancers which appear in a period up to 5 years cannot be counted as associated with RT. Radiotherapy is inevitably connected with irradiation of organs and healthy tissues located outside the tumour; however, conformal techniques may help to reduce these side effects. Most observed cancers induced by radiation were within the margins of the target volume (by definition this is an area up to 5 cm from the tumour border).

It should be emphasized that ionizing radiation is only one of the factors affecting the risk of cancer induction alongside those such as smoking and other environmental loads that may influence the frequency and risk of developing subsequent cancers not included in the study. Apart from that the SEER database itself is not an infallible source of data because cases of secondary cancer are often not correctly recorded in it (some of them have not been entered at all; there is also a lack of their correct substantiation, in particular when the data derive from a death certificate that does not include detailed information).

Schneider [27] made an attempt to estimate the risk of occurrence of secondary cancers depending on the level of the administered dose of radiation in patients treated with conformal radiotherapy (3DCRT, IMRT) and proton beam irradiation. With this aim radiotherapy of 23 patients with prostate cancer was planned according to the following outline: 7 patients with fourfield technique, 8 patients with IMRT technique and 8 patients with the use of proton therapy (two lateral fields). The range of total doses applied in the research was from 70 to 100 Gy, with application of a fractional dose of 1.8 Gy. The risk of occurrence of cancer induced by radiation was presented as a function of dose and probability of tumour control. The authors showed that administered doses of 100 Gy in comparison with 70 Gy caused greater risk of developing secondary cancer by 18.4%.

On the other hand, the increased risk of development of secondary cancer associated with a higher dose may be recompensed by achieving greater local effectiveness of therapy. The authors show in the summary that the risk of induced cancer occurring after application of a dose of 100 Gy may be even smaller than the risk that we may expect when applying a dose of 70 Gy. To summarize, further increase of the dose level may intensify induction of carcinogenesis but at the same time increases the probability of tumour control (TCP – tumour control probability).

Proton therapy is in this case a method of choice because it reduces almost by half the risk of secondary cancers in comparison with photon therapy. The results of this study show that escalation of the dose in the treatment of prostate cancer increases the risk of inducing secondary cancer. The risk of secondary cancers with the application of a dose of 100 Gy for IMRT in comparison with 3DCRT with the application of 70 Gy may be increased by a maximum of 25%. The estimated number of post-radiation solid tumours would increase from 34/10 000 to 43/10 000. However, considering the higher percentage of cure with the application of higher doses, it may be assumed

that the escalation of the dose creates a significantly higher chance for cure. The use of protons in this situation reduces almost twofold the risk of secondary cancer in comparison with 3DCRT, which means that this form of irradiation would give the greatest potential therapeutic benefit.

## CONCLUSIONS

The choice of the method of treatment for prostate cancer is usually dictated by the effectiveness of the proposed treatment and potential side effects. Irradiation treatment is connected with a small risk of inducing cancer. Considering the age structure of treated patients, it can be assumed that from the practical point of view this risk can be omitted. However, in future, together with the increased survival of patients and more frequent qualification for treatment at younger age, it may be necessary to consider the assessment of the described risk in the strategic approach.

Because there still exists a whole range of ambiguities concerning the assessment of results of irradiation treatment, it is necessary in future to create a systematic prospective programme aimed at determining the risk of cancer induction by radiation.

## References


1. Shipley WU, Thames HD, Sandler HM: Radiation therapy for clinically localized prostate cancer. A multi-institutional pooled analysis. JAMA 1999; 281: 1598
2. Hanks GE, Hanlon AL, Pinover WH et al: Survival advantage for prostate cancer patients treated with high-dose three-dimensional conformal radiotherapy. Cancer J Sci Am 1999; 5: 152
3. Hodgson D, Warde P, Gospodarowicz M: The management of locally advanced prostate cancer. Urol Oncol 1998; 4: 3–12.
4. Baade PD, Youlden DR, Krnjacki LJ: International epidemiology of prostate cancer: geographical distribution and secular trends. Mol Nutr Ford Res 2009; 53: 171–84.
5. Shimizu Y, Mabuchi K, Preston DL et al: Mortality study of atomic-bomb survivors, implications for assessment of radiation accidents. World Health Stat Q 1996; 49: 35–40.
6. Boice JD: Cancer following medical irradiation. Cancer 1981; 47: 1081.
7. Kato H: Radiation-induced cancer and its modifying factor among A-bomb survivors. Princess Takamatsu Symp 1987; 18: 117–24.
8. Calabrese EJ, Baldwin LA: Defining hormesis. Human Ex Toxicol 2002; 21: 91–7.
9. Martland HS: The occurrence of malignancy in radioactive persons, a general review of data gathered in the study of the radium dial painters, with special reference to the occurrence of osteogenic sarcoma and the interrelationship of certain blood diseases. Am J Cancer 1931; 15: 2435.
10. Bongers V, Braakhuis BJ, Tobi H et al: The relation between cancer incidence among relatives and the occurrence of multiple primary carcinomas following head and neck cancer. Cancer Epidemiol Biomarkers Prev 1996; 5: 595–8.
11. Lutz WK, Fekete T: Endogenous and exogenous factors in carcinogenesis, limits to cancer prevention. Inter Arch Occup Envir Health 1996; 68: 120–-5.
12. Yu CX, Amies CJ, Svatos M: Planning and delivery of intensity modulated radiation therapy. Med Phys 2008; 35: 5233–41.
13. Hall EJ, Wuu CS: Radiation induced second cancers, the impact of 3D CRT and IMRT. Int J Radiat Oncol Biol Phys 2003; 56: 83–8.
14. Brown JM: The effect of acute x-irradiation on the cell proliferation kinetics of induced carcinoma and their normal counterpart. Radiat Res 1970; 43: 627–53.
15. Westlake S, Cooper N: Cancer incidence and mortality: trends in the UK and constituent countries, 1993 to 2004. Health Stat Q 2008; 38: 33–46.
16. E G A Aird: Second cancer risk, concomitant exposures and IRMER (2000), The Br J Radiol 2004; 77: 983–5.
17. I.C.R.P. Radiation and Your Patient: A Guide for Medical Practitioners. Annals of the ICRP, 2001; 31.
18. Ding GX, Duggan DM, Coffey CW: Accurate patient dosimetry of kilovoltage conebeam CT in radiation therapy. Med Phys 2008; 35(3): 1135-44.
19. Pan T, Mawlawi O: PET/CT in radiation oncology. Med Phys 2008; 35: 4955–66.
20. Harison RM: The estimation of second cancer risk following radiotherapy: a discussion of two models. Biomed Imaging Interv J 2007; 3: 1–7.
21. Movsas B, Hanlon AL, Pinover W, Hanks GE: Is there an increased risk of second primaries following prostate irradiation? Int J Radiat Oncol Biol Phys 1998; 41: 251–5.

22. Neugut AI, Habibul A, Robinson E, Ennis R: Bladder carcinoma and other second malignancies after radiotherapy for prostate carcinoma. Cancer 1997; 79: 1600–4.
23. Brenner DJ, Rochelle E, Curtis MA et al: Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. Cancer 2000; 88: 398–406.
24. Pickles T, Phillips N: The risk of second malignancy in men with prostate cancer treated with or without radiation in British Columbia, 1984-2000. Radiother Oncol 2002; 65: 145–51.
25. Kendal WS, Eapen L, MacRae R, Malone S, Garth N: Prostatic irradiation is not associated with any measurable increase in the risk of subsequent rectal cancer. Int J Radiat Oncol Biol Phys 2006; 65: 661–8.
26. Moon K, Stukenborg JG, Keim J, Theodorescu D: Cancer Incidence After Localized Therapy for Prostate Cancer. Published online in Wiley InterScience 2006 (www.interscience.wiley.com): 991–8.
27. Schneider U, Lomax A, Besserer J, Pemler P, Lombriser N, Kasser-Hotz B: The impact of dose escalation on secondary cancer risk after radiotherapy of prostate cancer. Int J Radiat Oncol Biol Phys 2007; 68: 892–7.