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

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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,