Radiation-induced second cancers in prostate cancer patients

Background

Radiotherapy is a commonly used, potentially curative treatment modality in patients with localised and locally advanced prostate cancer. The development of a radiation-induced second primary cancer is a serious long-term side effect of radiotherapy treatment. Prostate cancer is the most common cancer in males in the UK, with a lifetime risk of one in eight. Since the advent of prostate specific antigen (PSA) testing, patients are diagnosed at an earlier stage in their disease and patients are surviving for longer following the diagnosis. The risk of radiation-induced second cancer is therefore particularly relevant for this group of patients.

Traditionally, a radiation-induced second cancer is considered as one which:
1) develops at least five years following irradiation
2) is of a different histological type to the original primary
3) was not present at the time of diagnosis of the original primary, and
4) develops within the field of radiation.

For prostate cancer, regions considered within the radiation field include the rectum, bladder, anus and the soft tissues of the pelvis. Two important caveats, however, must be borne in mind when considering the diagnosis of radiation-induced cancer. Firstly, patients may develop second cancers as a result of genetic and environmental factors (e.g. smoking or dietary factors) rather than due to radiotherapy. As such it should not automatically be assumed that a previously irradiated patient who develops a second cancer has done so because of the radiotherapy. Secondly, although the traditional diagnosis of a radiation-induced second cancer is one which develops in an ‘in-field’ region, patients are exposed to radiation doses far beyond the field edge (traditionally considered as the 50% isodose), and these lower doses could also result in radiation-induced second cancers.

The vast majority of the clinical evidence regarding second cancer risk from radiotherapy is retrospective. Studies comparing second cancer risk in irradiated prostate cancer patients and prostate cancer patients managed with other techniques (e.g surgically treated patients) are considered here. Most studies examine the risk of second rectal and/or bladder cancers as these are the most commonly identified second cancers observed to occur within the radiation field in prostate cancer patients. Studies require very large numbers of patients in order to have sufficient power to detect real differences between patient groups. Such large patient numbers are often available from registry data (e.g SEER – Surveillance Epidemiology and End Results databases) which generally contain tens of thousands of patients. One of the problems with registry data, however, is that the data is often less complete than institutional databases. For example, registry data often does not contain information about smoking status, and so important confounders may be missed. Registry data is often less complete in older patients. Data from single institutions may often contain more details about potential confounding factors, but the far smaller patient numbers mean that the power of these studies is more limited in detecting true differences between patient groups.

Clinical studies including older radiation techniques

Although there is a lot of variability in existing studies, several of the large registry studies with long term follow-up suggest that, compared to non-irradiated prostate cancer patients, irradiated prostate cancer patients are at increased risk of second cancers, and that this risk increases over time. For example, comparing second cancers in irradiated patients with surgically treated patients, Brenner et al used SEER registry data to estimate that the risk of a radiation-induced second solid cancer at any site (i.e. including second cancers beyond the radiation field) in irradiated patients was one in 290 after two months of follow-up, one in 125 for patients followed up beyond five years and one in 70 for patients followed up beyond 10 years. For second rectal cancer specifically, irradiated patients were at increased risk compared to surgically treated patients but this risk was only significant after 10 years of follow-up (when there was a 105% increase in risk in irradiated compared to surgically treated patients). For second bladder cancer specifically, a significant increase in risk was identified in irradiated patients compared to surgically treated patients of 15%, 55% and 77% beyond two months, five years and 10 years of follow-up respectively. While an increase in risk from early on in the follow-up period is not generally attributed to radiotherapy, this may be the result of surveillance bias, whereby patients with urinary symptoms following radiotherapy are investigated and incidental second bladder cancers are identified. Beyond five years of follow-up, the traditional time from which radiation induced tumours may be diagnosed, the risk increases further and beyond 10 years the increased risk is higher once again. While this, and similar studies, provide an indication of second cancer risk in irradiated patients, it must be remembered that the studies with the longest durations of follow-up contain patients treated with older radiation techniques. For example, the Brenner et al study mentioned above, included patients diagnosed with prostate cancer between 1973 and 1993. In this and similar studies, larger radiation fields and lower doses were used than are routine in current practice. In addition, cobalt-60 techniques were often used. Furthermore, many of these patients were diagnosed before the routine use of PSA, and so a larger proportion of patients would have had more advanced disease than patients diagnosed currently.

The relevance of the risk estimates from these studies, for modern day patients frequently treated with smaller fields in the setting of localised disease and with higher doses, is therefore called into question.

Intensity modulated radiotherapy

A few clinical studies have specifically examined second cancer risk in patients treated with more modern radiotherapy techniques. Of particular recent interest is the impact of intensity modulated radiotherapy (IMRT) on the risk of...
second cancer. There have been traditional theoretical concerns that the ‘low dose bath’ resulting from multi-field IMRT may expose a greater volume of normal tissue to low dose, potentially cancer-inducing radiation compared to more traditional dose distributions (figure 1). The three existing clinical studies that examine second cancers and IMRT suggest that there is no increase in the risk of second cancers in patients irradiated with IMRT compared to the general population or non-irradiated prostate cancer patients.17-19 These studies, however, contain far fewer patients (ie less than 1,000 patients in each study) and have much shorter follow-up than the studies concerning older radiation techniques. It is therefore too soon to draw firm conclusions about the clinical impact of IMRT on second cancer risk.

In the absence of reliable clinical data regarding second cancer risk following IMRT, theoretical planning studies aim to address this issue. These may consider both the change in dose distribution from IMRT, as well as the increase in out of field dose which results from the increase in monitor units and resultant increase in head leakage that accompanies IMRT. The method in which second cancer risk should be estimated in planning studies, however, is a matter of debate.20 Several different methods of second cancer estimation exist and none of them are a perfect fit to the clinical data, and the errors associated with risk estimation are often large.21 While some of the early planning studies suggest that IMRT would result in a very large relative increase in risk of second cancer risk,18,21,22 more recent studies suggest that risk is either similar to that from 3D-conformal techniques or, if increased in absolute terms the increase in risk is very small.25-28

Brachytherapy

There is also interest in whether prostate brachytherapy, which results in a very sharp dose fall off, could result in lower risks of second cancer compared to external beam techniques (EBRT). As with IMRT, the existing clinical data contain smaller patient numbers and shortened durations of follow-up compared to studies examining older external beam techniques. The majority of the data is highly encouraging, and suggests that patients treated with brachytherapy are not at increased risk of second cancer compared to non-irradiated prostate cancer patients.17,18,20-21 Importantly, it is only the largest registry study to compare second cancers in brachytherapy patients and non-irradiated prostate cancer patients that demonstrates that both brachytherapy monotherapy and combination brachytherapy-EBRT resulted in an increased risk of bladder cancer after six months of follow-up, between six months and five years of follow-up and between five and 10 years of follow-up.11 In addition, compared to non-irradiated prostate cancer patients, patients treated with combination brachytherapy and external beam radiotherapy were found to be at increased risk of rectal cancer after 10 years of follow-up.11 This underlines the importance of adequate patient numbers and long durations of follow-up. As above in relation to IMRT, larger patient numbers and longer follow-up are necessary before firm conclusions can be drawn about the impact of brachytherapy on second cancer risk.

Conclusions

In conclusion, there is clinical evidence that suggests that irradiated prostate cancer patients are at an increased risk of second cancer compared to non-irradiated prostate cancer patients. This risk appears to increase over time. This evidence, however, includes patients treated with older, less clinically relevant techniques and important confounding factors, such as smoking and other environmental risk factors, may not have been included in the analyses, introducing potential bias into these conclusions. The clinical evidence regarding more modern techniques, including IMRT and brachytherapy, is encouraging and so far is less suggestive of an increased second cancer risk compared with studies evaluating older techniques. However, the patient numbers and follow-up in studies evaluating more modern techniques are insufficient to allow firm conclusions to be drawn. The potential risk of radiation-induced second cancer should be remembered when considering treatment options for prostate cancer patients, particularly those who are younger and with early stage disease, who are likely to have a long survival following treatment.

References

Figure 1
Comparison of dose distributions for 78Gy in 39 fraction intensity modulated radiotherapy (IMRT) and 3D-conformal radiotherapy (3D-CRT) in prostate cancer. The ‘low dose bath’ that results from IMRT has led to concerns that a larger volume of tissue is exposed to lower-dose potentially cancer inducing radiation. The colour wash key on the right displays total dose in Gray.