LATE SIDE EFFECTS AND COMPLICATIONS IN BREAST CANCER PATIENTS TREATED BY POSTOPERATIVE RADIOTHERAPY.

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INTRODUCTION

The value of postoperative radiotherapy in patients with operable breast cancer has been a subject of a long lasting controversy. This modality was found to be very effective in preventing locoregional recurrences but its impact on the survival has been unclear. Recent metaanalises of clinical trials have indicated that radiotherapy may improve survival in some patients, but it may also increase non breast cancer mortality (Cuzick et al., 1994, Cuzick, 1987; EBCTCG, 1995).

In postmastectomy irradiation the treatment volume is large and irregular and it includes the chest wall and regional lymph nodes: internal mammary, supraclavicular and apex of the axilla. Within this volume there are several organs and tissues which may potentially be damaged by radiation: the skin and subcutaneous tissue, ribs and clavicle, lymphatic vessels, brachial plexus and the shoulder joint. The lung and heart are in direct proximity to the treatment volume and, depending on radiotherapy technique, these organs may also receive significant doses.

There are several methodological problems in assessing the risk of late side effects and complications. In the first place, it is very difficult to estimate the incidence of sequelae in retrospective analysis with the exception of very severe complications which require treatment, and hospitalisation or are lethal. The real incidence of mild or asymptomatic effects can only be estimated, if a prospective protocol is implemented and carefully followed. This should include assessment and scaling the effects at regular intervals and performing additional studies, if necessary, e.g. chest X-ray to document radiation changes in the lung or asymptomatic rib fracture. Secondly, all of the late radiation effects show the existence of the latent period when both the incidence and severity tend to increase with time. Some patients die from the metastatic disease shortly after the treatment, in others follow-up is not long enough to cover the latency period of a particular complication. Thus, the incidence of late radiation changes should be calculated only with the actuarial methods. Thirdly, there are some complications, like induced secondary cancers or radiation-related heart disease, which may be difficult to separate from those occuring in the absence of radiotherapy. The risk of these complications requires evaluation either by using randomised clinical trials involving the control group not treated with irradiation, or by employing epidemiological techniques within a large population-based registry (Bentzen and Overgaard, 1994; Bentzen, 1993; Turreson, 1989).

The aim of this presentation is to review the current knowledge concerning the late radiation effects and complications in breast cancer patients with special emphasis on radiation induced heart deaths and secondary neoplasms.

TYPE OF LATE RADIATION EFFECTS AND COMPLICATIONS OCCURRING IN BREAST CANCER PATIENTS AND FACTORS INFLUENCING THE RISK

1. Possible late sequelae and complications of postmastectomy radiotherapy in breast cancer patients include: teleangiectasia, subcutaneous fibrosis, soft tissue necrosis, arm oedema, brachial plexopathy, impaired shoulder movement, rib fracture, lung fibrosis, radiation related heart disease, and carcinogenesis (Table 1).

2. Factors that may influence the incidence and severity of these effects include: radiation therapy factors (dose, dose distribution within the treated volume, and the fraction size), interaction with other treatment modalities (i.e. surgery and chemotherapy), and individual radiosensitivity of the patients.

Treatment volume in postmastectomy irradiation	Tissue and organs within high dose volume or in close proximity.	Possible late effects and complications
Chest wall	skin and subcutaneous tissue	teleangiectasia and fibrosis
	ribs, clavicle	bone necrosis
Lymph nodes:		
-supraclavicular,	lymphatic vessels	arm oedema
-apex of axilla,	brachial plexus	brachial plexopathy
	shoulder joint	"frozen shoulder"
-parasternal	lung	pneumonitis and fibrosis
	heart	radiation induced heart disease
	controlateral breast, other tissues	carcinogenesis

Table 1. Late side effects and complications in breast cancer patients treated with postoperative radiotherapy.

Effect	36.5 Gy/12 fractions 73 patients	42 Gy/22 fractions 66 patients	p-value
Teleangiectasia grade ≥ 2	29%	12%	0.009
Fibrosis grade ≥ 2	67%	5%	$<10^{-8}$
Lung fibrosis grade ≥ 2	32%	17%	0.04
Arm oedema	45%	33%	0.14
Rib fractures	19%	2%	0.0003
"Frozen shoulder" grade ≥ 2	40%	11%	$2x10^{-5}$

Table 2. Incidence of various late effects after two protocols for postmastectomy radiotherapy using different doses per fraction. Modified from SM Bentzen and M. Overgaard (Bentzen and Overgaard, 1994).

2.1. In general the risk of late radiation sequelae increases with the total dose. Dose distribution associated with the quality of radiation and technique are also important in some situations. In most of the effects the importance of the dose per fraction was demonstrated in clinical studies (Table 2). With the use of large fractions a significant increase in the incidence of late changes and complications was found for the following effects: teleangiectasia, fibrosis, soft tissue necrosis, impaired shoulder movement, rib fracture, lung fibrosis, and brachial plexus damage. In these effects, the low alfa/beta ratios between 2-5 Gy, and latency periods ranging from 2-15 years were calculated from clinical data (Table 3), (Bentzen and Overgaard; 1994, Bentzen; 1993, Fletcher; 1991, Powell et al.; 1990).

Tissue	Effect	α/β ratio (Gy)	LT_{90} (years)
subcutis	fibrosis	1.9	3.2
vasculature	teleangiectasia	2.8	2–15
lung	fibrosis	3.6	?
bone	necrosis	3	<3
muscle /vasculature/ cartilage	"frozen shoulder"	3.5	3.9
nerve	brachial plexopathy	<5.3	?

Table 3. α/β ratios and latency period for late effects after postmastectomy radiotherapy. Modified from SM Bentzen (Bentzen, 1993).

2.2. Modern treatment of operable breast cancer usually involves a combination of surgery, radiotherapy, and systemic adjuvant chemo/or hormonal therapy. There is some clinical evidence that these modalities may have a combined effect on the treatment-related morbidity. The extent of the surgical removal of axillary nodes is related to the incidence of arm oedema which is increased by radiotherapy. The extent of tumour excision in the breast conserving therapy influences the cosmetic effect, an important endpoint in patients treated with this method. Concomitant application of radiation and chemotherapy increases the incidence of several radiotherapy related effects such as arm oedema, subcutaneous fibrosis, rib fracture, symptomatic pneumonitis and poor cosmesis in patients treated with breast conserving therapy (Table 4-6), (Fowble, 1992;

Harris and Morrow, 1996). The interaction between radiation and anthracyclines resulting in heart damage is of special interest (Hju Yiannakis and Yarnold, 1996).

Radiation dose	Incidence (%)		
	without CT	with CT	Total
≤ 50 Gy	0.4%	3.7% p=0.002	1.3%
> 50 Gy	3.2%	7.9% p=N.S.	5.6% p=0.004
Total	0.6%	4.5% p<0.0001	1.8%

Table 4. Incidence of brachial plexopathy in relation to radiation dose and use of chemotherapy. Modified from JR Harris and M Morrow (Harris and Morrow, 1996).

Radiation dose	Incidence (%)			
	4 MV	p Value	6 or 8 MV	Total
≤ 45 Gy	0.4 %		0%	0.2%
>45-<50 Gy	1.4%	N.S.	0.8%	1.3%
≥ 50 Gy	5.7%		0%	5.3%
Total	2.2%	0.05	0.4%	1.8%
Use of CT				
	without CT		with CT	
≤ 50 Gy	0.5%		2.3% p=0.01	
> 50%	4.7%		7.4% N.S.	

Table 5. Incidence of rib fracture in relation to radiation quality, dose and use of chemotherapy (CT). Modyfied from JR Harris and M Morrow (Harris and Morrow, 1996).

Use of CT	Incidence %	p-value
without CT	0.6%	
with CT	3.3%	0.001
sequential CT	1.3%	
concurrent CT	8.8%	0.002

Table 6. Incidence of radiation pneumonitis in relation to the use and sequencing of chemotherapy. Modified from JR Harris and M Morrow (Harris and Morrow, 1996).

2.3. Clinical observations have shown that within a group of identically treated patients there is a large variability in the incidence and severity of radiation sequelae in normal tissues (Bentzen and Overgaard, 1994; Turesson, 1990). This variability may be explained only in part by the random nature of cell killing by radiation and some predisposing factors, including age, and a coexisting disease, e.g. collagen vascular disease, diabetes mellitus or infection. An important factor contributing to this phenomenon is a considerable variability in intrinsic cellular radiosensitivity from individual to individual which may be genetically dependent. There are several genetic syndromes associated with hypersensitivity to radiation confirmed by *in vitro* radiosensitivity tests. The best known example ataxia teleangiectasia (AT) is particularly interesting while considering the breast cancer patients radiosensitivity. The frequency of AT heterozygotes in a normal population has been estimated to be 1%. These individuals have an increased *in vitro* radiosensitivity of fibroblasts and also have an increased risk (approximately 8 times) of developing breast cancer. Therefore the frequency of AT gene (connected with higher radiosensitivity) occurs in breast cancer patients with a much higher frequency than that in general population and it was calculated to amount to 8-18% (Andersen, 1996, Norman et al., 1992). These findings have generated a great interest in testing of individual radiosensitivity with the hope that it will make it possible to modify the radiotherapeutic schedules according to the results of these tests. Indeed some studies have shown a correlation between the *in vitro* sensitivity of fibroblasts and clinical normal tissue reaction (Johansen et al., 1994). On the other hand, lack of a correlation between radiosensitivity of various cell types has been reported. Also, in breast cancer patients there was no significant correlation between the severity of radiation changes for two different tissues (e.g. teleangiectasia and subcutaneous fibrosis) in the same patient (so called intra-patients variability) (Bentzen et al., 1993). At present, it seems unlikely that a single and simple assay (e.g. micronucleus assay on peripheral blood lymphocytes) could be used as a reliable predictor for late radiation effect in several tissues.

RADIATION INDUCED HEART-DISEASE AND CARDIOVASCULAR MORTALITY IN PATIENTS TREATED WITH POSTMASTECTOMY IRRADIATION

Radiation injury to the heart may have different presentations including: early (exudative) and late (constrictive) pericarditis, pancarditis, valvular and conduction defects, a coronary arteries disease and myocardial infarction. Although the heart was initially considered radioresistant, radiation heart injury was found to be a clinically important problem, especially in long term survivors after radiotherapy for Hodgkin's disease (Levitt, 1995).

In breast cancer patients, particularly in those with left sided tumours, the heart may receive a significant dose depending on the radiotherapy technique used. In several reports increased non-breast cancer mortality was found in irradiated patients in comparision with those treated by mastectomy alone (Haybittle et al., 1989; Host et al., 1896, Jones and Ribeiro, 1989; Rutqvist and Johansson, 1990).

This problem was addressed in the retrospective analysis performed in the group of 1885 patients with breast cancer treated at the Centre of Oncology in Kraków between 1952-80. Surgery alone was used in 1068 patients, and 817 patients were irradiated postoperatively.

The orthovoltage technique was used in 650 patients, who received doses of 36-40 Gy in 20 fractions; the remaining 167 patients were treated with ^{60}Co technique with a dose of 50 Gy in 25 fractions. The treatment volume included the chest wall and regional lymph nodes in all patients. Adjuvant systemic therapy was not applied. The cumulated incidence of non-breast cancer deaths was calculated using life tables method (Table 7).

Treatment method	Number of patients	Risk of non-breast cancer death		Chi^2
		10 years	20 years	
Surgery alone	1068	6.3%	16.4%	1.520 N.S.
Surgery+ RT	817	4.7%	9.9%	

Table 7. Comparison of the risk of non breast cancer death in patients treated with surgery alone and with postoperative radiotherapy (RT).

After 10 years, the risk of non-cancer death was 6.3% in patients treated with surgery alone and 4.7% in patients irradiated postoperatively. After 20 years, these rates rose to 16.4 % and 9.9% respectively. The difference however, was not statistically significant. Thus, our analysis did not show any increased risk of non-breast cancer mortality in the irradiated patients. This result should, however, be treated with caution because of the retrospective nature of the study. In fact, patients treated with surgery alone were slightly but significantly older (mean age 54 years) than those irradiated postoperatively (52 years). It was also not possible to distinguish cardiac deaths from other non cancer deaths (Korzeniowski, 1991). More reliable data come from the analysis of clinical trials. Long term results of several clinical trials assessing the value of postoperative radiotherapy demonstrated a significant increase in non-breast cancer deaths in the irradiated groups, which was due to an excess of cardiac mortality. The increase in cardiac deaths became apparent in long term survivors, usually in the second decade of observation, and was more pronounced in older (>60 years) patients and in patients with left sided breast cancer (Haybittle et al., 1989; Host et al., 1896; Jones and Ribeiro, 1989; Rutqvist et al., 1992).

Observations from individual trials were subsequently confirmed in two metaanalyses performed by Cizick et. al. (Cuzick et al., 1994; Cuzick et al., 1987). Data from metaanalyses suggest that an increased risk of cardiac death may be related to radiation quality (orthovoltage), total dose and volume of the heart irradiated and to the use of high dose per fraction (Table 8).

Centre	RT quality	Dose (Gy)	Number of fractions	P-value for risk of cardiac death
Manchester Quadrate	250 KV	35-40	15	0.06
Manchester Peripheral	250 KV	32.5-42.5	15	0.02
Oslo II	^{60}Co	50	20	0.07
Heidelberg	^{60}Co	54	30	0.05
Stockholm	^{60}Co /electrons	45	25	0.28

Table 8. Increased risk of cardiac death in relation to radiation quality and dose in patients irradiated postoperatively within randomised trials who survived over 10 years. Modified from J Cuzick et al. (Cuzick et al., 1994).

A detailed analysis was performed with this respect in patients treated in the Stockholm trial and the importance of the radiotherapy

technique was confirmed. Increased cardiac mortality was found only in patients who received high doses to a large volume of the heart (patients with left sided cancer treated with ^{60} Co tangential beams) (Rutqvist et al., 1992). Fuller et. al. compared doses given to the heart and coronary arteries with old orthovoltage and modern megavoltage techniques and found that in the megavoltage mode the total dose to the heart was significantly reduced, but in patients with the cancer of the left breast the part of the left ventricle and the left anterior descending coronary artery may have received relatively high doses (Fuller et al., 1992).

The radiation induced heart disease is the most serious complication of postmastectomy irradiation. With modern radiotherapy equipment, the use of electron beams, careful individual treatment planning, the irradiation of the myocardium may be avoided. Thus with appropriate techniques and the use of conventional fractionation (2 Gy) the risk of radiation induced heart mortality should be very low.

SECONDARY NEOPLASMS AFTER POSTMASTECTOMY RADIOTHERAPY

Another possible and important complication of postoperative radiotherapy in breast cancer patients is the induction of secondary malignancies, and, in particular cancer of the contralateral breast. Breast tissue was shown to be sensitive to radiation carcinogenesis. The risk of radiation induced breast cancer is influenced by dose and age at exposure. The risk of carcinogenesis increases linearly with the dose up to 10 Gy, but at the therapeutic range (45 – 50) it seems to be small, probably due to the process of cell inactivation. In relation to age, the highest risk occurs in females exposed to radiation in adolescence, with increasing age the risk declines and seems to be very low for women over 40 years of age. The dose to the opposite breast from postoperative radiotherapy was estimated to be in the range of 1 to 3 Gy, therefore, it could lead to the induction of contralateral breast cancer. The risk is difficult to assess because patients with breast cancer, even if not irradiated, are at a higher risk of developing cancer in contralateral breast with a relative risk between 2.0 and 4.0 (Harris and Morrow, 1996).

Other radiation induced tumours which may develop within tissues irradiated during postoperative radiotherapy include soft tissue and bone sarcomas, the cancer of the lung, the oesophagus skin and the thyroid.

In the study performed at the Kraków Centre of Oncology in the group of 1885 patients (described above) the long term risk of contralateral breast cancer and malignant tumours in other sites was assessed (Table 9 and 10). Cumulative incidence of contralateral breast cancer after 10 years was 4.4% for patients treated with surgery alone and 2.8% for the irradiated group; 20-year rates were 6.5% and 4.1%, respectively ($p<0.05$). The risk of developing a neoplasm in other sites was: 8.6% after 10 years in the surgical group and 5.4% in the combined modality group; the respective rates were 11.4% and 9% ($p<0.05$). Thus, the incidence of contralateral breast cancer and other malignancies appeared to be higher in patients treated with surgery alone, which may be explained by the older age of patients in the surgery alone group.

Localization	Treatment method	Number of patients	Incidence		Chi^2 p-value
			10 years	20 years	
Contralateral breast	Surgery alone	1068	4.4%	6.5%	4.93
	Surgery + RT	817	2.8%	4.1%	p<0.05
Tumours in other sites	Surgery alone	1068	8.6%	11.4%	4.68
	Surgery + RT	817	5.4%	9.0%	p<0.05

Table 9. Incidence of cancer of contralateral breast and tumours in other sites in patients treated with surgery alone and with postoperative readiotherapy (RT).

Localization	Surgery alone	Surgery + RT
Stomach	6 (15.4%)	2 (9%)
Colon	3 (7.7%)	3 (13.3%)
Lung	2 (5.1%)	1 (4.5%)
Skin	4 (10.3%)	3 (13.6%)
Uterine cervix	4 (10.3%)	3 (13.6%)
Endometrium	6 (15.4%)	0
Ovary	2 (5.1%)	2 (9.1%)
Other	12 (30.7%)	8 (36.4%)
Total	39 (100%)	22 (100%)

Table 10. Comparison of localization of secondary tumours, in patients treated with surgery alone (1068 patients) and with postoperative radiotherapy (817 patients).

There were two cases of lung cancer in patients treated with surgery alone and one in the irradiated group. Skin cancer developed in one patient within the irradiated chest wall. The distribution of tumours in other sites was, in general, similar in both groups, with the

exception of the cancer of endometrium. This difference, too large to be explained by older age, probably appeared by chance. Neither sarcoma nor leukaemia cases were found in this material (Korzeniowski 1991).

A number of other studies have also addressed the risk of secondary neoplasms after post mastectomy radiotherapy. Boice et al. studied the incidence of contralateral breast cancer in a cohort of 41109 patients with breast cancer diagnosed between 1935-82 (Boice et al.; 1992). In patients who survived for at least 10 years they found a small, but marginally significant increase of risk of contralateral breast cancer (RR=1.33), associated with the use of postoperative radiotherapy. This risk was evident in patients less than 45 years of age when treated (RR=1.59), but not in older patients (RR=1.01). On the contrary, a large study from Denmark, which included 56560 patients treated between 1943-78, did not show any increased risk of contralateral breast cancer in the irradiated patients (RR=1.04) (Storn et al.; 1992). The data from the literature suggests that the risk of radiation induced contralateral breast cancer, if it exists, is very small. Boice et al. estimated that for younger (<45 years) patients the risk of contralateral breast cancer within 15 years is about 11% without radiotherapy and about 12% with radiotherapy. After 30 years, it was calculated to increase to about 22% and 25% respectively. Thus, especially in young patients, the dose to the contralateral breast should be reduced to the possibly lowest levels. Various technical solutions of how to minimise the dose to the contralateral breast have recently been proposed (Epstein et al., 1996).

Rare but undoubtedly radiation-induced tumours are sarcomas of the soft tissue and bone which develop within the treated area. In a series from France, 9 of 7620 patients irradiated for breast cancer developed sarcoma within the irradiated volume. The mean latency period was 9.5 years and the cumulative incidence was estimated to be 0.2% after 10 years and 0.43% after 20 years (Taghian et al., 1991). Lymphangiosarcoma arising in lymphoedema of the arm is a very rare tumour, and it is not like other sarcomas, a true postirradiation neoplasm, since it occurs also in patients treated with surgery alone. However, this complication may be regarded as a radiation related since radiotherapy increases the incidence and severity of the arm oedema.

An increase in the incidence of lung cancer was also found in patients irradiated for breast cancer. The relative risk for the period of 10 years or longer following treatment was estimated to be 1.8, which corresponds to approximately 9 cases of radiotherapy-induced lung cancer per year among 10.000 breast cancer patients whose survival time was over 10 years (Levitt, 1995, Taghian et al., 1991).

Finally, a small increase in the incidence of acute nonlymphocytic leukemia in breast cancer patients treated with radiotherapy was suggested in one report, but not confirmed in others (Inskip et al., 1994). This requires further studies and may be of importance in patients receiving adjuvant chemotherapy with alkylating agents, which were also reported to have a leucemogenic effect.

CONCLUSIONS

Studies on late radiation effects in patients treated with postmastectomy irradiation have proved very useful in the understanding of radiobiological processes. The crucial importance of dose per fraction, as well as interactions between radiotherapy and chemotherapy or surgery in relation to incidence and severity of radiation sequelae, has been well documented in clinical materials. The most significant complication of postoperative radiotherapy in breast cancer patients has been a long term increase in cardiac mortality. As suggested by recent overviews that increase in cardiac mortality and, to lesser extent, secondary malignancies, may possibly offset the survival advantage from postoperative radiotherapy.

The optimisation of radiotherapy techniques involving beam energies, field arrangements, shielding of critical normal tissues and the use of conventional fractionation, should in future greatly diminish radiotherapy related morbidity.

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