

## Commentary • Komentarz

### Breast cancer treatment risk factors with special reference to experience in developing countries

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*It is essential for physicians and surgeons who are involved in the treatment of breast cancer to develop a better appreciation of the problems encountered when radiation therapy is given. In this brief review special emphasis is placed on treatment toxicity and patient quality of life and on the assessment of treatment success.*

*The aim of radiation therapy (RT) is local recurrence prevention. With the introduction of RT after breast conserving surgery the local recurrence rate fell from 25-40% to the current rates of 6-8%. In developing countries, such as Tunisia, the rate may be as high as 15% due to <sup>60</sup>Co – teletherapy without the use of a treatment planning system as well as with the initial advanced stage of the disease in those countries.*

*An important additional endpoint of treatment is the quality of life and long-term toxicity. Severe deterioration of RT toxicity is caused by intramammarian seromas and extended tissue defects, certain concomitant chemotherapy protocols and the deliberate use of parasternal lymph node irradiation. Age, however, does not influence the radiogenic toxicity.*

*We conclude that apart from local control and five-year survival these additional endpoints, i.e. defining toxicity and quality of life, have to be accepted by all physicians involved in breast cancer treatment.*

#### Ryzyko związane z leczeniem raka piersi ze szczególnym uwzględnieniem sytuacji w krajach rozwijających się

*Lekarze zaangażowani w proces leczenia chorych z rakiem piersi muszą zdawać sobie sprawę z problemów wynikających ze stosowania radioterapii. W niniejszej pracy przedstawiono pokrótce zagadnienia związane z wpływem odczynów po napromienianiu oraz jakości życia na ogólną ocenę wyników leczenia.*

*Radioterapia (RT) ma na celu zapobieganie wznowom miejscowym. Wprowadzenie radioterapii jako uzupełnienia leczenia oszczędzającego pozwoliło zmniejszyć odsetek wznów miejscowych z 25-40% do 6-8%. Niemniej w państwach rozwijających się, takich jak Tunezja, odsetek ten sięga nawet 15% ze względu na stosowanie teleterapii z użyciem kobaltu <sup>60</sup>Co z pominięciem jakichkolwiek technik planowania, jak również ze względu na znaczne zaawansowanie choroby w momencie rozpoznania.*

*Dodatkowe istotne elementy rzutujące na ocenę wyników leczenia to jakość życia i obecność późnych odczynów po radioterapii. Te ostatnie nasilają się znamienne w sytuacji miejscowego gromadzenia się płynu surowiczego w piersi, przy współistnieniu rozległych ubytków tkankowych, w połączeniu z jednoczesnym stosowaniem niektórych rodzajów chemioterapii oraz w razie planowego naświetlania przymostkowych węzłów chłonnych. Stwierdzono, że wiek chorych nie wiąże się z nasileniem toksyczności radioterapii.*

*Podsumowując można stwierdzić, że w ocenie wyników leczenia raka piersi należy brać pod uwagę nie tylko wyleczenie miejscowe i przeżycia pięcioletnie, ale również późne odczyny po napromienianiu i jakość życia chorych.*

**Key words:** breast cancer, radiotherapy, toxicity, quality of life

**Słowa kluczowe:** rak piersi, radioterapia, toksyczność, jakość życia

#### Introduction

Breast cancer is the most frequently encountered malignant disease in women and provides a challenging daily problem for doctors, patients and healthcare systems in the western world. The incidence rate of this malignancy is rising steadily and in Germany 1 of 9 women will have breast cancer. In the USA the comparable figure is 1 in 8 women. An optimistic outcome requires diagnosis in its early stages. Many patients receive radiotherapy,

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either alone or in combination with chemotherapy and/or surgery, and thus the knowledge of risk factors associated with radiation therapy is important. This paper also emphasises the continuing wide differences between developed and developing countries, and reviews the recent experience of one of us [JS] on an IAEA radiation oncology expert mission to Tunisia.

## Epidemiology

### Incidence

Breast cancer is predominantly a problem in the developed world (Table I), and the number of patients in South America, Africa or South East Asia is much lower than in Europe and the USA.

**Table I. Average annual age-standardised (world) incidence rates (ASR) per 100,000 for the registration period 1993-97 for selected registry populations [1]; incidence rates for comparison, for prostate and breast cancers. It is seen that even for developed countries with a smaller incidence of prostate cancer, the breast cancer rates are still high in the range 75-95 per 100,000 females**

Registry	ASR per 100,000 population	
	Prostate	Breast
USA, SEER registries	107.0	92.1
Canada	80.2	78.5
Denmark	29.9	81.3
Netherlands	53.9	85.6
England, UK	39.6	74.4
Algeria, Algiers	5.4	21.3
Zimbabwe, Harare	30.7	20.3
Argentina, Concordia	31.3	55.1
Colombia, Cali	42.2	37.3
Thailand, Bangkok	6.8	25.5
Vietnam, Ho Chi Minh City	3.8	13.6

### Migration

Migration of women from regions in South America, Africa and South East Asia to northern developed countries changes the originally lower risk dramatically – equalling the figures in the native developed populations within five years: according to the findings of the World Health Organization [2]. Thus, the style of living, eating habits, use of drugs or life's stress might have a decisive role in the development of breast cancer.

### Socioeconomic status

On the other hand, the figures for breast cancer may serve as an indicator for a population's socioeconomic progress. Recent epidemiological data from the Maghrebini Republic of Tunisia have demonstrated that a change towards a more westernised lifestyle influences breast cancer incidence in younger women. This data is now comparable with those of the southern European country of Portugal.

## Screening and early diagnosis

Large differences remain in the healthcare systems and the health education of the populations of Western Europe and of North African countries. For example, with elaborate breast cancer screening programs with serial mammography studies the average tumour diameter at diagnosis in Germany is 1.1 cm, while the comparable figure in Tunisia is 5.1 cm. This leads to a drastically inferior prognosis. At a tumour diameter of 1 cm about 25% of the patients are already affected by subclinical metastatic spread of the disease whilst at 5 cm nearly all the patients are suffering from distant, clinical or subclinical metastases resulting in a very poor five-year prognosis.

## Role of radiation therapy

The role of radiation therapy is directed primarily towards local control of the disease, with systemic treatments such as chemotherapy and hormonal therapy given to enhance the 5-year or 10-year survival rates. In the early days of breast conserving surgery without radiotherapy, local recurrence rates were in the range 25-40%. After the introduction of postsurgical radiotherapy to the entire remaining breast tissue these figures fell to the current rates of 6-8%. Hence the quality of radiation therapy in terms of equipment and treatment planning can be measured by the evaluation of the local recurrence rates.

On a recent expert mission to Tunisia for the IAEA, one of us [JS] found that the local recurrence rate in radiotherapy was one of the decisive factors used to evaluate the quality of treatment. Whilst the recurrence rate in Kiel is 3%, in one of the Tunisian institutions visited, the local recurrence rate after breast conserving treatment and radiotherapy was as high as 15%. It was then determined that treatment by <sup>60</sup>Cobalt teletherapy without any use of a treatment planning system, as well as the advanced stage of disease, was the determining factor for this unsatisfactory result.

## Risk factors

Local control is not the sole endpoint assessment following radiation therapy for breast cancer. In this primarily curative treatment, long-term toxicity and quality of life are of major interest. This is not always well recognized in developed countries, as a consequence of inferior treatment results. Also, perhaps due to the fact that all individual specialists playing a part in breast cancer treatment modalities, do not have sufficient knowledge of risk factors relating to treatment.

In a classical interdisciplinary treatment for breast cancer the results of radiation therapy depend upon the skills of the gynaecologist, the medical oncologist, the radiologist and also the general practitioner. To enhance their knowledge the risk factors associated with radiation oncology must be known.

## Seromas and tissue defects

A total of 104 consecutive patients with breast conserving treatment were irradiated in Kiel. The techniques were planned individually based on a CT dataset. All the acquired slices were evaluated with regard to seromas, larger tissue defects or organized hematomas exposing risk factors for radiation therapy.

In 38/104 patients, seromas and tissue defects measuring more than 2 cm were detected. 21/38 had already complained of discomfort in the breast and scar induration prior to radiation therapy. Thereafter, 36/38 patients had similar symptoms. 23/38 rated the cosmetic result worse than immediately after surgery. Of 66/104 patients without drainage problems only 9/66 had symptoms and only 4/66 rated the cosmetic result as worse.

We conclude that seromas and tissue defects after breast conserving carcinoma treatment increase the rate of side-effects during radiation therapy and lead to deterioration of the cosmetic results.

Pre-therapeutic applied CT allows to puncture hidden seromas and provides individual adaptation of the irradiation technique so as to avoid overdosage caused by tissue defects. Therefore, CT should be performed on all patients prior to radiation therapy and surgeons should continue to drain the resection hole and the axilla, preferably with active suction [3-5].

## Age

Cancer in elderly patients is frequently treated below standards. Arguments for such a strategy include poor prognosis, higher toxicity and costs. Therefore, in Kiel we have evaluated the standards of treatment in elderly women with breast cancer and assessed the results of their radiation therapy. Of the 218 consecutively treated breast cancer patients 83/218 were older than 64 years. Their 5-year survival rate was 77.1% and their rate of local recurrence was 1.2%. No significant age group specific differences in surgical and radiotherapy treatment and in toxicity could be found.

We therefore conclude that the prescription of curative treatment is independent of age and should be given to elderly as well as younger patients. A policy of discriminating the elderly is by no means justified [6].

## Systemic treatment

In general, the combination modality of radiochemotherapy is well tolerated and does not cause major problems. For the radiation oncologist however, gemcitabine and anthracyclines pose a certain risk. Whilst anthracyclines elevate the skin toxicity and can sometimes lead to severe erythema in grade 3-4, the concurrent application of gemcitabine and radiation therapy might lead to severe general toxicity. In the most severe cases this may cause sudden death [7]. Thus, as a precaution, radiotherapy should never be applied regularly together

with these agents except within controlled clinical trials [8].

## Parasternal lymphnode irradiation

In former times radiation oncologists used to treat the parasternal lymph node chain with single fields of 6 MV or <sup>60</sup>Cobalt photons. However they underrated the toxicity of such a treatment to the heart and to the coronary arteries and also overrated its therapeutic benefit. All institutions now continuing such a protocol should urgently revise their strategy. It is now common belief that irradiation of the parasternal lymph nodes is only necessary in selected cases at risk and that the long-term toxicity at the heart by far surpasses the therapeutic benefit [9].

## Conclusions

As well as the accepted treatment endpoints, such as local control and five-year survival rate, additional endpoints are needed which define toxicity and quality of life. Methods to measure the individual quality of life and the influence of late toxicity of treatment are available and have been applied in controlled trials [10]. These will enhance our ability to measure the treatment sequelae not only in a curative setting, but for assessment of treatment in a palliative setting [11].

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