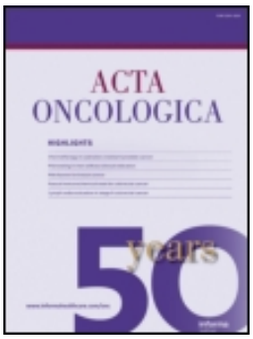

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**EDITORIAL**

# Radiation induced brachial plexopathies

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A daily challenge for the radiation oncologist is to prescribe the optimal radiation dose that will produce the maximal probability of local tumour control, and, at the same time, minimal risk for complications. The radiation dose needed to control tumours is commonly close to that tolerated by normal tissues. Thus, the level of normal tissue morbidity will often determine the cure rate that may be achieved.

Both tumour cure and serious normal tissue damage depend on the extent of cell depopulation. Every clonogenic stem cell has to be killed in the tumour to achieve long lasting tumour control. Clonogenic cells, however, have to survive in normal tissues to avoid serious normal tissue damage. Tolerance doses are not absolute values and they are different for different tissues.

The tolerance dose depends on various biological (patient-related) and treatment-related factors. To patient-related factors belong e.g. age and obesity. Obesity can affect the development of lymphoedema [1,2]. Co-morbidities like diabetes, hypertension, or collagen vascular diseases [3,4] will also influence the normal tissue reactions. Treatment-related factors are, e.g. chemotherapy, surgery, radiation quality, irradiated volume, number and size of fractions and overall treatment time [5]. This gives a very complex picture that needs to be individually assessed before prescribing the treatment.

The time of expression of the cellular injury after irradiation is variable from one tissue to another. The severe acute reactions in rapidly proliferating tissues can readily be observed and may thus rapidly result in changes in radiotherapy schedules that may be 'too hot'. This is not the case for late injuries that can occur long after completion of therapy. Late reactions are often defined as side effects that occur after a latency period of more than six months. They are generally caused by depletion of slowly proliferating cells with a slow rate of cell loss and renewal, e.g. in central or peripheral (Schwann cells) nervous tissue [6,7], blood vessels (endothelium) [8,9], dermis (fibroblasts) [10–12] and bones [13]. In general, fractionation of irradiation will spare acute reactions because of the compensatory proliferation in the epithelium of the skin or mucosa.

There is no solid scientific rationale for the "standard fractionation" frequently used today for radiation therapy, which are five fractions per week with breaks on weekends. It results from a standard working pattern of five days per week that changed from six days per week in the sixties. Hypofractionation was initiated around the mid-sixties to ease the burden for the cancer patients who had to come to hospital to be treated every day. It also helped to save machine time because of a lack of resources. This was considered acceptable according to the best clinical and radiobiological knowledge available at that time.

The brachial plexus lies deep within the root of the neck and at the apex of the axilla (about 3 cm below the skin) and direct palpation of the brachial plexus is impossible. There is no optimal treatment set-up or technology available today that can avoid including the nerve plexus in the treatment volume when the lymph nodes in the axilla or in the supraclavicular area are the target of the treatment. The techniques commonly used to treat the axilla and supraclavicular nodes in adjuvant radiotherapy all have significant disadvantages, including underdosing the deeper nodes, excessively irradiating normal tissues, or producing undesirable hot spots [14]. The nerves entering the upper limb provide important functions, such as: sensory innervations of the skin and deep structures, e.g. the joints; motor

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innervations to the muscles; influence over the diameters of the blood vessels by the sympathetic vasomotor nerves; and sympathetic secretomotor supply to the sweat glands. When the peripheral nervous system is included in the treatment volume adverse affects such as plexopathies can occur. Brachial plexopathy is commonly related to breast cancer, lung cancer, lymphoma, or metastatic tumour, or it can be induced by radiotherapy. Pain occurs in the majority of patients with brachial plexus involvement and may precede both motor and sensory loss by months or even years. When the upper plexus is invaded by tumour, pain usually begins in the shoulder and is associated with shooting or electrical sensations in the thumb and index finger. When the lower plexus is involved, it begins in the shoulder and radiates into the elbow, arm, and medial forearm, and into the fourth and fifth digits.

Radiation-induced plexopathy is usually not histopathologically diagnosed today. The definitive diagnosis of myelithis needs pathologic confirmation [10], but this cannot be obtained in most cases. The diagnosis rests on supportive information, and is usually based on the clinical symptoms of the patients. The radiation-induced side effects on different peripheral nerves, however, can be quite subtle at the beginning and if they appear years after treatment, neither the patients nor the doctor might recognise them as significant. The exact physiopathology of plexopathies still remains unclear, however, vascular alterations, radiation induced fibrosis in the environment of the nerves and direct effect on the Schwann cells appears to play an important role. Recurrent or metastatic tumour must be ruled out.

Techniques such as EMG, CT-scan, MRI [15] and PET [16] have been used to distinguish neoplastic and radiation-induced plexopathies. Compared with tumour-related plexopathy, radiation damage to the brachial plexus seems to cause less severe pain, and is initially distributed in the upper division of the brachial plexus.

Peripheral nerves are generally thought to be more radioresistant than the central nervous tissue. The $TD_5$ is probably between 57 and 61 Gy and the dose resulting in $TD_{50}$ is probably 68 to 73 Gy for the spinal cord [17]. Peripheral and cranial nerve damages after radiation therapy have been reported for the optic nerve, hypoglossal nerve, oculomotor nerve, abducens nerve, recurrent laryngeal nerve and peripheral nerves of the extremities. Similarly, tumour invasion or irradiation to the pelvis and abdomen may result in plexopathies and pain in the lumbar, sacral (lumbosacral plexus with pain experienced in the abdomen and upper regions of the leg. Specific plexopathy in the sacral region may result in pain in the perineal and perirectal regions.

Substantial amounts of data have been acquired during the past four decades on late side effects of radiotherapy and in particular on brachial plexus neuropathy. More than 300 publications can be found when a MEDLINE search is performed to find relevant literature regarding radiation-induced plexopathies after breast cancer treatment. Between 1970 to 1980, the publications basically focused on describing the clinical pictures of the lesions but some had already discussed cell population kinetics [18]. In most of the early reports, the patients had been treated at a time when peripheral nerves were regarded as very resistant to radiation damage and the neurological complications came as a surprise. Several reports showed that the occurrence of brachial plexus neuropathy was highly dose and fractionation dependent with a steep dose-response relationship [19,20]. The lack of a unified system of reporting radiation doses and volumes was, however, a problem. Different centres defined the given radiation dose in an arbitrary way and the treated volume without specific anatomic correlation.

The focus in most of the publications during the past three decades has been on the treatment volumes and fractionations. In attempts to increase the therapeutic ratio, various fractionation schedules have been used but not many prospective studies have been carried out. However, tumour cell sensitivity to radiotherapy is the most important factor to determine whether the treatment will be successful and the patient will be cured without major side effects. Retrospective studies have not shown strong clinical evidence demonstrating that individual differences in normal tissue sensitivity influence the response of tumours to radiation [5]. It is impossible to predict the late effects in normal tissues from acute reactions [21]. There seems to be a trend, however, towards better local control in patients with severe acute radiation reaction of normal tissue [22]. There is still a lack of clinically reliable predictive assays for both tumour and normal tissue radiation sensitivity [23,24], which would help the clinician to avoid severe radiation induced morbidity and result in individualised dose prescriptions. Every patient is unique! Patients treated with identical radiotherapy schedules show substantial variation in the degree of acute and late normal tissue reactions. The variability is still unexplained but may be related to individual differences in cellular radiosensitivity, partly determined by genetic variations and partly by unknown epigenetic factors [25].

The extent and frequency of late permanent damage depends on many factors including the dose, volume and time since treatment [26]. The

latency period is shorter with increasing dose. The overall treatment time is believed to have no significant influence on the development of late damage [27], however, this is still debated [28]. Late effects are more sensitive to changes in the size of dose per fraction, and acute reactions are more sensitive to changes in the rate of dose accumulation. The dose-response curves seem to be steeper for late effects than for tumour control [29,30]. Higher individual doses per fraction and larger volumes of the tissue irradiated are associated with an increase in the incidence and severity of late complications plexopathies [21,31–33].

A variety of strategies have been tested for the management of radiation-induced fibrosis such as superoxide dismutase, pentoxifylline, tocopherol, a combination of tocopherol and pentoxifylline [34], however, with mostly disappointing results. There is no reliable evidence to support the hypothesis that hyperbaric oxygen (HBO2) therapy slows or reverses radiation induced plexopathies in a substantial proportion of affected individuals, although improvements in sensory threshold offer some suggestion of therapeutic effect [35]. Pain relief might be achieved with neurolysis but no recovery of either the sensory or the motor function impairment has been shown.

Survival is the most important but not the only criteria of the usefulness of a treatment. For example, it has been accepted for a long time that postoperative radiotherapy after mastectomy improves both local and regional control but it has just recently been shown to increase the survival as well in breast cancer patients [36,37]. There is still no generally accepted consensus on the indication and the technique of irradiation that should be used and controversy still exists about what volumes should be irradiated [38]. In particular, uncertainties exist in whether the supraclavicular and internal mammary nodes should be included in adjuvant treatment.

One might ask the question whether radiotherapy is safe enough today to be used without causing serious late side effects for the patients that can be cured? What kinds and levels of side effects are acceptable as the price the patients might be willing to pay to increase the likelihood to survive cancer? The increasing use of combined radiation, chemotherapy, and surgery has led to an increased incidence of acute and late complications. The complications are, in general, similar to those seen with each modality alone, but can occur with increased incidence. Proper selection of drugs perhaps can lead to enhanced local control by radiotherapy and/or surgery, as well as eradicating microscopic distant metastases, without increased normal tissue injury. This however remains to be shown! Adjuvant paclitaxel after doxorubicin is commonly used in high-risk breast cancer patients resulting in a prolonged delay of the onset of radiation therapy after breast-conserving surgery. Concurrent delivery of breast irradiation with paclitaxel would allow for earlier initiation of radiation. Additional studies are needed to determine optimal timing, long-term toxicity, and potential benefits of concurrent radiation therapy and paclitaxel [39]. New surgical techniques such as sentinel node biopsies may allow nodal staging without major surgical intervention in the axilla and this can open new possibilities for more optimal combination of radiotherapy and surgery in the management of the axilla.

In Sweden approximately 37% of the breast cancer patients undergo adjuvant radiotherapy after surgery and 60% of all breast cancer patients get irradiation at some point during their lifetime [40]. This therapy accounts for a significant proportion of the workload in a modern radiotherapy department. Short treatment schedules would therefore have the attraction of more convenience for both the patients and the physicians but raise concerns about an increased risk of late effects. The expected enhancement of the incidence of breast cancer during a 15-year of period is about 20% in Sweden [41]. The tendency of the early detection of smaller and smaller tumours results in fewer patients with spread disease to the lymph nodes at diagnosis. This would mean that fewer patients would be regarded as high-risk patients. The need of adjuvant postoperative radiotherapy after breast conserving surgery would increase in the future due to the expected enhancement of the incidence of early breast cancer. However studies are going to identify subgroups of patients with low risk for recurrence that might not need adjuvant radiotherapy. All together, a lower number of patients who will need radiotherapy might balance the expected increase in the incidence.

## Summary

There is overwhelming evidence today that fraction sizes of more than 2 Gy produce a high frequency of brachial plexus neuropathies as shown by Galecki et al. in this issue of Acta Oncologica [42]. As the symptoms of plexopathies are progressive and irreversible and successful treatment methods are still lacking, prevention is a necessity. Due to the subtle nature of the symptoms and the long delay before onset it is important that these should be recognised by clinicians as a potential late side effect of radiation given many years earlier and not necessarily representing a signal of tumour regrowth.

Most tumours are actively proliferating and rapidly responding. Their fractionation response is most likely to be similar to that of acutely responding normal tissues. From this point of view, hypofractionation would provide a therapeutic disadvantage. Of course a highly localised dose (e.g., in stereotactic radiotherapy) may compensate this biological disadvantage. There seems to be, however, a tendency towards a 'return of the hypofractionating schedules' today in two of the most frequent cancers such as breast and prostate cancer. New hypofractionated schedules have been proposed due to new radiobiological data, suggesting high fractionation sensitivity of the prostate cancer [43]. There is, however, no radiobiological rationale for returning to hypofractionation in the treatment of breast cancer. The discussion appears to be economical and a short cut to reduce waiting lists.

In the coming decades a larger population of breast cancer patients can expect longer survival than those diagnosed 30 years ago. Therefore, and because of the subtle nature of some of the plexopathies and the long delay before onset, five years of follow-up should be the minimal time when evaluating late side effect of any treatment [44]. Well-designed patient questionnaires might help when oncology departments lack both the manpower and the funding to execute the long follow-ups requested [45].

There seems to be a lifelong risk in the development of late side effects after radiotherapy [31,46,47], when the given radiation dose is high enough to eradicate all cancer cells. An increased awareness of the long latency period and the wide spectrum of different side effects of treatment are essential for the management of all cancer patients treated with radiotherapy, even with lower doses.

It took decades for radiotherapy specialists to understand that long-term follow-up was needed for assessing any radiotherapy schedules. Similar approaches do not seem to be governing chemotherapy or even many combination therapies with radio- and chemotherapy. There is an obvious risk that the same mistakes made in early years of radiotherapy will be repeated in other modalities.

Recently (November 2005), the Swedish Association of the County Councils, responsible for healthcare in Sweden, decided to economically compensate about 200 breast cancer patients with the most severe problems from hypo-fractionated radiotherapy given during the 1980s.

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