

TIMESCALE OF EVOLUTION OF LATE RADIATION INJURY AFTER POSTOPERATIVE RADIOTHERAPY OF BREAST CANCER PATIENTS

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Purpose: To evaluate the incidence and prevalence of various signs of late morbidity, their time of appearance and pattern of progression during an observation period up to 34 years in breast cancer patients treated with postoperative radiation therapy after radical mastectomy.

Methods and Materials: A group of 71 breast cancer patients received in 1963–1965 aggressive postoperative telecobalt therapy to the parasternal, axillary, and supraclavicular lymph node regions after total mastectomy and axillary clearance. None of the patients received chemotherapy either prior to, or after the irradiation as part of their primary treatment. The prescribed dose to the three lymph node regions was 44 Gy in 11 fractions. Only two of the three fields were treated per day. This total dose was given in 16–17 fractions over 3–4 weeks. Because of the overlap of the supraclavicular and axillary fields, the dose received by the brachial plexus was not the dose that was prescribed. A retrospective dose calculation showed that the total dose to the brachial plexus was 57 Gy, delivered as a complex combination of 1.8 Gy, 3.4 Gy, and 5.2 Gy fractions. This cohort of patients has now been followed to 34 years and the late side effects of the treatment evaluated and scored.

Results: This series is unique in the literature. There is no comparable report of a detailed long-term follow-up in a homogeneously treated group of patients with such a high survival, especially among the younger women, where it is almost 50% at 30 years. This is the reason that they were able to develop some of the very slowly evolving injuries. There was progression of many of the late effects in the period between 5 and 34 years. The more serious morbidities have increased progressively over the whole 34-year follow-up period. Ninety-two percent of the long-term survivors have paralysis of their arm. Other neurological findings included unilateral vocal cord paralysis among 5% of the patients, who developed the disease after a median time of 19 years. All of them were left-sided, indicating a mediastinal involvement of the recurrent nerve. Local recurrence or the appearance of a new primary tumor infiltrating or causing pressure on the recurrent nerve were vigorously investigated and excluded as possible causes of these symptoms.

Conclusion: The greatest risk for all cancer patients is the inadequate treatment of their disease, because this is inevitably lethal. The aggressiveness of the therapy and the acceptable risk of complications must therefore be balanced against the risk of recurrence. The neuropathy seems to be closely linked to the development of fibrosis around the nerve trunks. The use of large daily fractions, combined with hot spots from overlapping fields contributed to the severity of the complications. © 2000 Elsevier Science Inc.

Radiation, Late morbidity, Breast cancer, Neuropathy, Fibrosis, Vocal cord paralysis.

INTRODUCTION

The gradual success of cancer treatment has led to longer patient survival. Unfortunately, this carries with it the penalty of providing a greater opportunity for late effects to appear, increase in severity, and impact on the quality of life of the patient. Cancer is a disease that requires a long follow-up to monitor any tumor recurrence and to fully understand the toxicity of any treatment.

The incidence of complications involving muscles and nerves increases with time after radiation (1, 2). Late damage becomes more severe, progresses with time, and usually cannot be halted or reversed. Several papers have been

published in which radiation-induced brachial plexus neuropathy (BPN) has been described (3–9). Radiation using large doses per fraction is less well tolerated by the brachial plexus than small doses per fraction (10). A couple of case reports have also been published on BPN after mantle radiotherapy to a dose of 40 Gy in 20 fractions for Hodgkin's disease (11, 12). Other nerves such as the phrenic nerve (11) and the recurrent nerve (13) can also be affected, leading to more subtle symptoms.

Most of the studies and conclusions about the evolution of BPN are based on follow-ups that do not extend more than 5 years, at which time it is often assumed that all the late effects will have been detected. It is important to test

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Table 1. Patient characteristics

Median age	55 years	(range: 33–78 years)
T1	25%	
≥T2	75%	
Nodal status	Node-negative	48%
	Node-positive	45%
	Not determined	7%
Side	Left	42%
	Right	58%
Median survival	All patients	12 years
	Node-negative	17 years
	Node-positive	9 years
	>55 years	9 years
	≤55 years	28 years

that assumption and to see whether more damage appears in late reacting tissues if the patients are studied for a longer period. If there is further progression beyond 5 years, either in incidence or in severity, it will obviously be important to pay particular attention to the follow-up interval when comparing morbidity reports from different trials that do not have the same overall time since treatment. Only long-term follow-up can determine the ultimate risks of radiotherapy.

In the early 1960s a University Hospital with an Oncology Department was first established in Umeå. This provided the only radiation resources for the northern geographic half of Sweden. Some patients received surgical treatment in their local hospital, but all were sent to Umeå University hospital for their radiotherapy.

The first case of BPN was observed in 1965 at the radiotherapy department in Umeå, 2 years after the start of a hypofractionated telecobalt treatment modality for postoperative treatment of breast cancer. A cohort of 71 patients treated with this technique from March 1963 to March 1965 was defined (14) and has been followed for 34 years. In the present paper we focus on the incidence and prevalence of fibrosis, vocal cord paresis, and Grade 3 and Grade 4 neuropathy. The time of appearance and pattern of progression of the damage has been analyzed.

METHODS AND MATERIALS

Patients

These breast cancer patients were treated with postoperative radiation therapy after radical mastectomy by a standardized ^{60}Co technique during the period March 1963–March 1965. The patient characteristics are presented in Table 1. All medical records of these 71 patients were still available and were reviewed. The patient files included details of the diagnosis and staging of the breast cancer and details of the surgery and the subsequent follow-up. No analyses existed for hormone receptor status or DNA analyses at that time. The records also included full details of radiotherapy (including the treatment record sheets and in all cases a photographic record of treatment positions, etc.). They document any concurrent illness, and provide comprehensive follow-up records and all correspondence. This

Table 2. Scales used to quantify morbidity

	Grade 3 (G3)	Grade 4 (G4)
Pain	Persistent and intense	
Strength	Persistent weakness	Paralysis
Sensory loss	Persistent paresthesia	Complete anesthesia
Mobility	>50% decrease from baseline capabilities	Paralysis

includes letters to and from consultants in surgery, neurology, radiology, orthopedics, and plastic surgery. The quality of the medical records was generally good and quite detailed but inevitably not complete in all cases.

All these patients were operated with total mastectomy combined with axillary dissection or sampling. None of the patients received chemotherapy neither prior to, nor after the irradiation as part of their primary treatment, but it was not withheld in case of metastasis, when it was found necessary. Almost all of the patients continued to be followed up at regular 3-month to 1-year intervals at the Oncology Department. Some patients were referred back to the surgeon who had operated on them. In those cases detailed correspondence was available and when the symptoms of the patients required it, they were referred back to the oncologists in Umeå.

The diagnosis of brachial plexus neuropathy was assigned in the present analysis when there were motor or sensory symptoms or physical signs present in a nerve root distribution in the arm on the treated side, with or without pain. The neurological manifestations could be paresthesia in the fingers or hands, hypesthesia, hypalgesia, disesthesia, paresis, hyporeflexia, and muscular atrophy. Pain was not always a feature although it was not uncommon in the BPN condition. In many cases, repeated fine needle biopsies were taken in an attempt to make the differential diagnosis between the possibility of malignant infiltration of the plexus region by a recurrent tumor mass and radiation-induced plexopathy. CT and MRI were not available in the early follow-up period and have not been used on the long-term survivors. Most, though not all, of the patients developing these symptoms were referred to a neurologist, and electromyography (EMG) was also carried out to confirm the diagnosis; however, in some cases there was an inconsistency between the clinical symptoms and EMG result.

The neurological damage is graded, using a system based on the information recently provided in the SOMA LENT scales (15). It is, of course, not perfect to use this scale on a retrospective analysis of patient files but we have found it to be feasible and useful. Table 2 demonstrates the scales that were used for Grade 3 or 4 morbidities. The records were not detailed enough to make a systematic evaluation of the extent of fibrosis in every patient. These data have simply been collected as presence or absence in the record and are not graded. The most massive fibrosis was usually seen in the supraclavicular fossa, as documented in the records and in many photographs.

In the present analysis an attempt was made to evaluate the latency of BPN from the time of completion of radiotherapy to the first symptoms of plexus injury and to differentiate between the different types and degrees of neurological lesions, including vocal cord paresis resulting from recurrent nerve damage. The incidence of the different morbidities is defined as the percentage of the 71 treated patients who developed the syndrome and prevalence as the percentage with the syndrome among patients still alive.

Radiation therapy technique

Postoperative radiation was delivered by a standardized ^{60}Co technique to the three regional lymph node areas through one axillary (A), one supraclavicular (S), and one parasternal field (P). The peak dose prescribed was 11 fractions of 4 Gy to each field. A dose of 4 Gy was given daily for 5 days a week, to a planned total dose of 44 Gy per field over an average overall time of 21 days (range 18–28 days). Only two of the three fields were irradiated each day. Thus $11 \times 3 = 33$ treatments were spread out over 17 irradiation sessions. The chest wall including the scar after the mastectomy was not included in the treatment fields.

The dose in the brachial plexus region was contributed both by the axillary field (A) and the supraclavicular field (S). These were treated with the patient in different positions. The arm was elevated when the axilla was irradiated, which may have increased the overlap of beams in the plexus, but the axillary beam was angled at 30° dorsally to the horizontal to reduce the overlap. When those fields that included the plexus were given on separate days, they contributed doses of 1.8 Gy from the axillary field or 3.4 Gy from the supraclavicular field. However, when they were irradiated on the same day the total dose increased to 5.2 Gy. Thus, the total dose to the brachial plexus was a combination of 17 treatments of 1.8 Gy, 3.4 Gy, and 5.2 Gy fractions and amounted to 54–57 Gy in the brachial plexus, because of the hot spot where the two fields overlapped. The sequence of the (A + S), (A + P), or (P + S) combinations varied from one patient to another. In addition there was a random variation in whether the 16 or 17 treatment sessions included 5 or 6 combinations of (A + S) in which the 5.2 Gy fraction was delivered. This gave rise to some variation in the cumulative radiation effect (CRE) values. The CRE formula was used in the initial reports and was recorded for each patient in the records. The median CRE value for the brachial plexus was calculated to be 2147 (range 1967–2200) and was considerably higher than the commonly recommended CRE value of 1800–1900. It was assumed for those retrospective calculations that the affected part of the plexus was located at an average depth of 3 cm below the surface of the supraclavicular field. The median field size of the supraclavicular field was 114 (range 69–168) cm^2 , the axillary field 126 (range 64–168) cm^2 , and the parasternal field 94 (range 65–127) cm^2 .

Table 3. Timescale of evolution of fibrosis, BPN, VCP, pain, and Grade 3 or 4 neurological damage

	Grade of damage	Time (years)			No. of patients (%)
		Mean	Min	Max	
Fibrosis	—	1.8	0.3	10.9	61 (86%)
BPN	—	4.2	0.3	18.9	45 (63%)
VCP	—	19	10.0	25.0	4 (5%)
Pain	> G3	3.1	1.2	13.2	19 (27%)
Strength	G3	5.4	0.4	22.3	37 (52%)
	G4	9.4	1.6	29.8	33 (46%)
Sensory loss	G3	6.4	0.4	23.5	24 (34%)
	G4	10.6	1.5	29.8	25 (35%)
Mobility	G3	6.2	1.3	26.1	36 (51%)
	G4	10.8	1.5	29.8	35 (49%)

RESULTS

The median survival for the whole group was 12 years and there was a threefold increase in the median survival in patients who were below the median age at treatment, relative to the older group (28 years versus 9 years). The 5, 10, 20, 30, and 34-year actuarial overall survival rates for the whole group are 81%, 59%, 38%, 25%, and 17% respectively.

The time course of evolution of injury is illustrated in Table 3 for fibrosis, BPN, vocal cord paresis (VCP), and Grade 3 or Grade 4 neurological symptoms. Sixty-one (86%) of the patients developed skin fibrosis. The mean time to develop fibrosis was 1.8 years, but the last patients recorded as developing the damage appeared at 11 years after treatment. Not all, but many of the patients with fibrosis developed BPN as well. The development of neuropathy is slower (mean time: 4.2 years). The last patient with BPN was recorded 19 years after the treatment. Unilateral recurrent nerve paralysis was found in 4 (5%) patients. It was detected by symptoms of hoarseness and then diagnosed by visual examination of the vocal cord. All of them were left-sided, indicating a mediastinal involvement of the recurrent nerve. The first patient with VCP appeared 10 years after radiotherapy and the last patient at 25 years. All of these patients were subjected to a thorough physical examination to determine whether the symptoms were the result of tumor recurrence or fibrosis in the mediastinum. Local recurrence or the appearance of a new primary tumor infiltrating or causing pressure on the recurrent nerve were vigorously investigated and excluded as possible causes of these symptoms.

Table 3 also shows that the mean time to develop Grade 3 neurological damage is beyond 5 years for strength, sensory loss, and mobility. The last patients developing Grade 3 damage were recorded between 22 and 26 years after the treatment was given. As might be anticipated, it takes even longer to develop Grade 4 damage. The mean time is about 10 years, but new cases could be detected even 30 years after irradiation. In some cases it was clearly stated in the

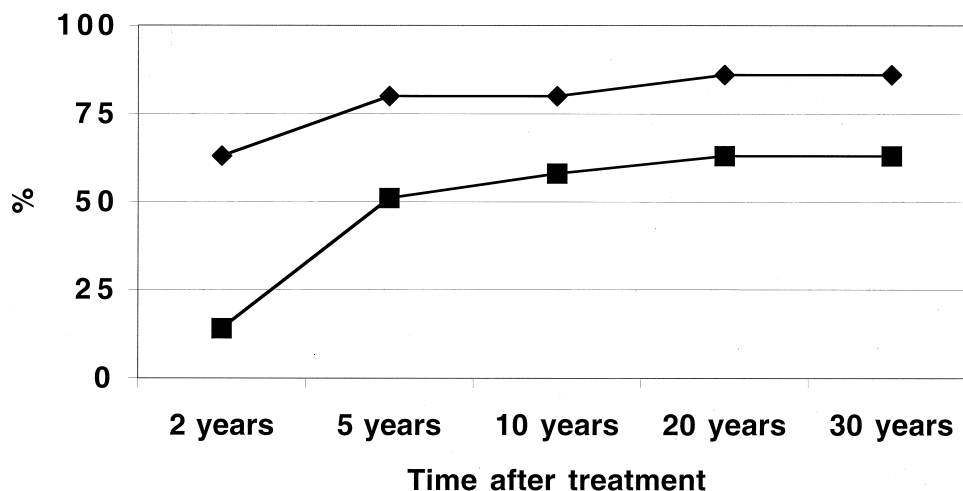


Fig. 1. Cumulative incidence of the first record of fibrosis (◆) and BPN (■) in a group of 71 breast cancer patients after hypofractionated irradiation. There is a slow evolution of the damage, especially for BPN.

patient files whether the patients still had some mobile function in the arm but no strength at all, which could explain the differences between the Grade 4 toxicity for strength and mobility.

Figure 1 illustrates the cumulative incidence of fibrosis and BPN at incremental times after treatment. Already 2 years after the irradiation 63% of the patients had fibrosis and 14% developed BPN. The incidence of both fibrosis and BPN increased beyond 10 years and reached its plateau about 19 years after treatment. By 34 years after radiotherapy, 86% of the patients had developed fibrosis and 63% neuropathy.

Figure 2 shows the prevalence of fibrosis, BPN, and paralysis of the arm among patients who are still alive at different time after treatment. At 5 years, less than one-quarter of the patients with fibrosis had paralysis of their

arm, but at 30 years after treatment most of the patients with fibrosis developed paralysis. The prevalence of paralysis increases very steeply after 10 years among the long-term survivors and progresses over the entire follow-up period.

The successive sections of Fig. 3 allow one to see the evolution of different aspects of Grade 3 and 4 neurological symptoms with time, associated with BPN. In all cases there was a progression of injury with time considerably beyond 5 years.

DISCUSSION

The present long-term follow-up of a homogeneously treated group of patients has provided some insight into the evolution of late effects after overtreatment with radiation.

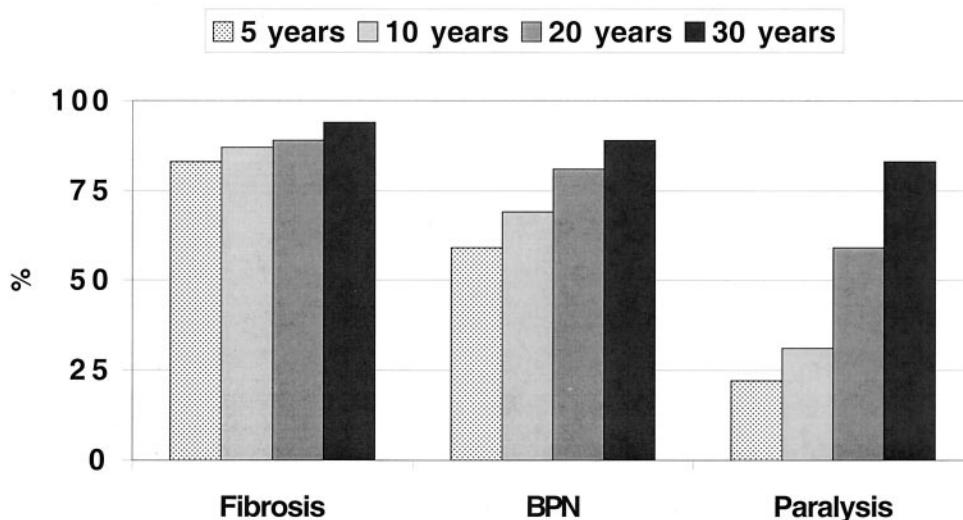


Fig. 2. Prevalence among survivors, at chosen intervals between 5 and 30 years, of fibrosis, BPN, and paralysis (Grade 4 damage of mobility). Most of the fibrosis had been recognized within 5 years but the progression to the first symptoms of BPN and especially to paralysis occurred much more slowly, over decades. By 30 years most of the survivors had severe neuropathies.

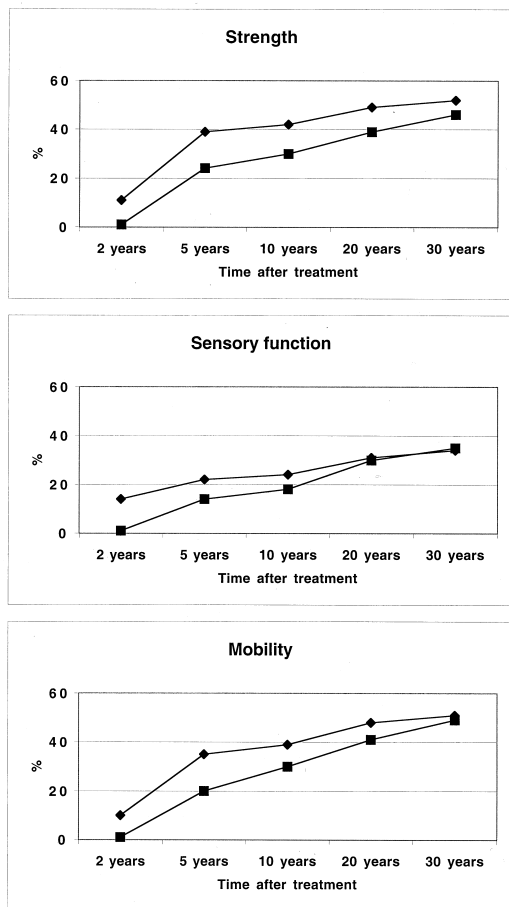


Fig. 3. Cumulative incidence of three different aspects of BPN over the intervals 2–30 years. The percent of the 71 patients originally treated is illustrated, showing Grade 3 damage (◆) usually progressing with time to Grade 4 (■).

There is no comparable long-term follow-up in a group with such a high survival rate, especially among the younger women where it is almost 50% at 30 years. The delayed incidence of neuropathy among these patients could develop because there were so many long-term survivors and these late morbidities could be detected due to the long follow-up period.

Our data show that 5 years is too soon to assess the total risk of Grade 3 and Grade 4 neurological damages. The damage is progressive over the whole observation period of more than 30 years and an evaluation at 5 years would have underestimated the incidence of the damage by 20% for BPN and 60% for G4 damage of mobility. The main reason for such a high incidence of neuropathy for these patients is a combination of the large dose per fraction and the extra effect due to the hot spots from the overlapping fields. The prescribed dose of 11×4 Gy would correspond to 59 Gy (if α/β is 4) and 66 Gy (if α/β is 2) given as 2 Gy per fraction. These patients were, however, treated according to the best knowledge that was available at that time when the risks for hypofractionation regimes were not understood and hypofractionation was adopted because of limitations in the resources available.

Case reports are appearing for patients treated with lower doses for Hodgkin's disease developing very late neurological damage such as BPN and bilateral diaphragm paresis (11, 12), supporting the theory of the very slow evolution of neurological damage that can appear decades after the irradiation. However, these patients' treatment regimes included vinca alkaloids, which are known to be neurotoxic and might have influenced the development of the neuropathy after the lower doses of radiotherapy.

Cancer is a fatal disease, which requires aggressive therapy, with agents that have a narrow therapeutic window between success and failure. The toxicity and the high survival among these patients may both be linked to the increased radiation effectiveness of this short high dose per fraction regime (5). This would not, however, be considered acceptable as a cost benefit ratio nowadays.

Over the last 34 years a great amount of clinical and radiobiological information has been acquired. The place of radiotherapy has become more firmly established as a curative, organ-conserving therapy used alone or in combination with surgery as the main local treatment of primary cancer. There are now many long-term survivors and therefore late side effects are of prime importance. The incidence of complications involving muscles and nerves increases with time after radiation (1, 16). Slowly turn over tissues attempt cell division many months and years after injury. Lost tissue is then replaced with fibrosis. In addition, the fibrous connective tissue becomes more permanent, dense, and inelastic, constricting the structures that it should be supporting. Nerve compression by radiation-induced fibrosis in the absence of tumor recurrence is the hypothesized mechanism for neuropathy in previous publications where the etiology is discussed (5, 17).

Our data confirm that the evolution of fibrosis and neuropathy is very slow. It occurs over decades and not all of the cases are detected at 5, or even 10 years after the treatment. The radiation-induced side effects on different nerves can be quite subtle at the beginning and if they appear years after the treatment, neither the patients nor the doctors may deem them significant. Such was the case for the patients with vocal cord paralysis. Their symptoms might not be easily associated with treatment factors of breast cancer given decades before (13).

Quality assurance and evidence-based medicine are concepts that are increasingly recognized as important to all aspects of medicine. The success of radiotherapy depends on the total radiation dose, which is limited by the tolerance of surrounding normal tissues. It is impossible to predict the late effects in normal tissues from acute reactions, in assessing the success of radiotherapy. It is therefore desirable that regimes that have been used many years ago, and perhaps have been replaced by new protocols, should nevertheless have long-term outcome reported as a basis for comparison of subsequent treatment regimes. In this way it is hoped that the evolution of late morbidity will be better understood and the lessons of the past can contribute to better treatments in the future (5). The

risk of late effects should be included in the decision as to the fraction size and the follow-up of patients treated with radiotherapy. Any tendency toward a return to the use of fraction-

ation schedules with fewer, larger doses for economical reasons in patients with potentially curative disease should be strongly discouraged.

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