

EDITORIAL

Peripheral nerves are sensitive to irradiation, Or: on the pitfalls from too short follow-up times

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Among radiotherapists, there has long-since existed an opinion that peripheral nerves were resistant to irradiation. In 1960, Clemetsen & Nelson [1], in their comprehensive review of the literature, state: “Nervous tissues, especially of adult animals, show a remarkable radio-resistance”. Ordinary text-books in oncology and neurology, as a rule, have ignored the radiation-induced injuries of peripheral nerves, and also, the length of latency for late effects [2–12]. Not even such a specialized text-book as “Complications of Cancer Management” [13] published in 1994, present any information about radiation-induced injuries on peripheral nerves.

This misconception about radiation and nerve injuries has been to the disadvantage of injured patients, since most medical doctors are not aware of the relationship between radiotherapy and nerve injuries. But there existed diverging information already prior to 1960. Janzen and Warren in 1941 [14], Linder in 1959 [15] irradiated the sciatic nerve of rats to a dose of 30 Gy in five days and found a focal nerve degeneration and scarring in 25% of cases when examined three to 11 months after irradiation. A later publication in 1961 [16] by Innes and Carsten reported that irradiation of the nerves of cauda equina of rats with a single dose of 35 Gy resulted in severe degenerative lesion in the nerves of all the animals after seven months.

With today’s knowledge, radio-resistance of peripheral nerves can be regarded as a myth. There are at least three explanations to this myth: 1. Before the

1950s, low-energy machines were used. They had poor penetration in tissues, and did therefore not reach deep-seated nerves, 2. Lower irradiation doses were more frequent before 1950 than after, and 3. Patients were usually followed for a relatively short period of time, usually only five years. Nerve injuries may occur after longer latencies. Moreover, survival was considered to be the one and only major interest in some publications, whereas side effects – such as injuries to peripheral nerves – were disregarded (or not published). The sensitivity of the spinal cord to irradiation was known since Boden’s publication in 1948 [17], but the sensitivity of peripheral nerves at that time was not well-known. Boden described the latency for irradiation injuries to the spinal cord varied from five months to five years. It was not until Ware et al. [18], in 1975, had shown that nervous tissue was more sensitive to large fractions than other normal tissues and tumour cell populations.

This is well illustrated by the numerous women injured by hypofractionated radiotherapy while treated for cancer of the breast. A review of the literature is presented below.

The first clinical report of neuropathy to plexus brachialis (BPN) in humans came in 1964, when the Swiss neurologist Mumenthaler [19] published eight cases that had been irradiated after surgery for cancer of the breast. Some of these patients had been given very high doses, and one of them as much as 3 000 roentgen (28.5 Gy) to the axilla in a single

dose! This corresponds to a late effect of 179 Gy EQD_{2Gy} (!).¹

Lesions to the plexus became evident with latency, sometimes more than 10 years after radiotherapy.

In 1965, Edelman et al. reported on "Rapid Radiotherapy for Inoperable Carcinoma of the Breast. Benefits and complications" [20]. Using a Cobalt 60 unit, they gave 25 Gy in two days (late effect = 71 Gy EQD_{2Gy}) to 42 women. Twenty five of them developed severe complications in the form of frozen shoulders, pulmonary fibrosis, lymph oedema of the arm, and necrosis of bone or breast, already after eight months. Thirty three of their patients died from their malignancies within 18 months, and only six were alive after 60 months, so not many of their patients lived long enough to develop lesions of the brachial plexus.

The next publication appeared in 1966, when the two Australian radiologists Stoll and Andrews [21] reported their observations in "Radiation-induced Peripheral Neuropathy". They used a 4 MV linear accelerator for two different schemes: either 63 Gy in 12 fractions (corresponding to a late effect of 104 Gy EQD_{2Gy}), or 58 Gy in 11 or 12 fractions (corresponding to a late effect of 96 or 90 Gy EQD_{2Gy}). Thirty three women with cancer of the breast were in the first group, and 44 in the latter.

Severe plexus complications were seen in 73% and 15%, respectively. Symptoms could develop 30 months after completion of radiotherapy.

A year later, in 1967, two reports on the same theme appeared. From Switzerland were presented five cases [22], and from France 14 [23]. None of these two articles gave any details about the radiotherapy.

In 1968, a report appeared from the Swedish city of Umeå [24]. It was written in Swedish. The results were published in English in 1972 [25]. The first sentence reads: "At our Department, a uniform radiotherapy was given post-operatively during the years 1963 through 1965" (our translation). The treatment was 40–50 Gy in 3–4 weeks; fractionation not specified (which excludes the possibility to calculate EQD_{2Gy}). Thirty three percent of "some 80 patients" developed plexus lesions.

Thus, in 1968, injuries to peripheral nerves caused by hypofractionation had been published from: Australia, France, U.S.A., Sweden and Switzerland (in alphabetical order).

From their 173 patients, Frischbier and Lohbeck [26] reported in 1970 that a total of 33% (53 patients) had developed BPN (among other severe complications), and that among those surviving more than six years, 72% had developed complete paralysis. The authors gave 30 Gy preoperatively, and another 30 Gy postoperatively to areas which included both the brachial plexus and the chest wall. They used 15 MeV electrons with 2 Gy/fraction (late effect = 60 Gy EQD_{2Gy}) to 3 Gy/fraction (late effect = 72 Gy EQD_{2Gy}).

Also in 1970, a report appeared from one of the Swedish Institutions which had initiated and continued to use hypofractionation [27]. That institution used fraction sizes of 5.5 Gy (late effect = 137 Gy EQD_{2Gy}) to 6.0 Gy (late effect = 146 Gy EQD_{2Gy}). Two hundred and thirty seven patients had been subject to that treatment regime with varying doses up to 81 Gy in 21 days. Forty one cases (17%) developed severe plexopathy. The lesions were dose dependent: all 10 patients who had received more than 60 Gy were paralysed in the arm on the treated side. The follow-up time ranged from two to 10 years.

In Table I (published also in [28]) is listed the cumulative number of women with BPN for the first eight articles (up to and through 1970) which have been published in the medical literature in chronological order.

Table I raises the question: "How many women must be injured before the medical profession realizes that hypofractionation is not acceptable?" When should the alarm bell have tolled?

By 1968, more than 100 women had been published, severely injured by hypofractionated radiotherapy. And yet, hypofractionated radiotherapy continued to be used. In one Scandinavian country, hypofractionated radiotherapy was started in 1985.

The dissertation by S. Johansson in Umeå, Sweden [29] summarizes in the year 2000 the situation in a very eloquent way. Some of the patients in Johansson's dissertation were originally presented by Westling et al. [24] in 1968. During the 32 years of additional follow-up, almost all surviving patients (92%) had developed severe BPN.

The data-base Pubmed today provides over 300 articles dealing with the dangers of hypofractionation [30,31].

The injuries to the nerves in the plexus are believed to be caused by either a fibrotic strangulation of the bundle, or direct injury to the nerve sheath, or both. Also, the endoneurion may be thickened, and there may be extensive loss of myelin, disappearance of axis cylinders, and hyalinization and obliteration of blood capillaries. Rarely was the

¹(EQD (Equivalent Dose) is Estro nomenclatura. The corresponding American term is NTD: Normalized Total Dose in 2 Gy/fraction. The formula reads: EQD_{2 Gy} = D(1 + d/[α/β])/(1 + 2/[α/β]), where D = total dose, d = daily dose and α/β = the ratio of intrinsic radiosensitivity to repair capability.

Table I. Publications reporting on injuries supposed to be caused by hypofractionated radiotherapy, listed in chronological order.

Year	Author/reference	No of cases with BPN/no. treated	Cumulative no. of cases injured
1964	Mumenthaler [19]	8/+	8
1965	Edelman et al. [20]	25/47	33
1966	Stoll&Andrews [21]	37/117	70
1967	Fallet et al. [22]	5/?	75
1967	Aullas [23]	14/?	89
1968	Westling et al. [24]	35/80	124
1970	Frischbier et al. [26]	57/173	181
1970	Notter et al. [27]	41/237	222

immobilisation of the arm due to muscular atrophy in the shoulder girdle. The injuries in Sweden caused by hypofractionated radiotherapy have been investigated and reported by the authors of this article [28].

The long-term somatic sequelae of oncologic therapy have not been given due attention until recently. Therefore, it is encouraging that both Acta Oncologica and the newly formed Organisation of European Cancer Institutes (OECI) have paid the matter timely consideration: Acta Oncologica in a symposium in Oslo in 2006 [32–47], and OECI in a symposium in Budapest in 2007 [48].

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