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40/42Gy in 13 Fractions: A Safe Dose for the Brachial Plexus

Gabriela Studer[1*], David Norbert Stocker[2], Karl Ferdinand Loewenich[1] and Christoph Glanzmann[1]

[1]*Department of Radiation Oncology, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland*

[2]*Grundstrasse 61, 6430 Schwyz, CH, Switzerland*

[*]**Corresponding author:** Gabriela Studer, Department of Radiation Oncology, University Hospital Zurich Raemistrasse 100 8091 Zurich CH – Switzerland, Tel: 41 44 255 39 31; Fax: +41 44 255 45 47; E-mail: gabriela.studer@usz.ch

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Abstract

Aims: The use of hypo fractionated irradiation of the whole breast has regained much interest after the publication of the results of large randomized trials showing equivalent results as using standard fractionation (START A and B, randomized START pilot trials, Canadian trial). Due to the relatively low numbers of patients treated with hypofractionation to the supraclavicular ±axillary (S/A) region, the question of the brachial plexus tolerance continues to be discussed.

Aim of this work was to assess the high grade long term tolerance of the brachial plexus in our patients treated with 13x 3.3Gy to the S/A lymph nodes, in order to contribute to the question of plexus tolerance.

Materials and Methods: Between 1967 and 1977, 130 female breast cancer patients underwent postoperative hypo fractionated radiotherapy at the University Hospital Zurich. The most used schedule was 13x 3.3Gy midline dose, 3x/week (n=124) to the S/A region applied by equally rated antero-posterior/postero-anterior portals. A first assessment of the cohort was performed in 1994, which has been updated in December 2013. Patients with a follow up period <5 years or loco-regional disease have been excluded in 1994 (n=4, all without plexopathy). Pre-radiation surgery consisted of radical mastectomy in 98% and breast conserving operation in 2% of all patients, including axillary dissection. Pathological stage was pT1/2/3/4 in 28/58/10/4%; with pN0/pN+ in 57/43%. The mean/median follow up time of the cohort was 28.1/26.6 years (range, 7.2-44.8).

Results: One grade 2 brachial plexus neuropathy was observed.

Conclusion: The long term follow up in our patients corroborates the hypothesis of a total mid plane dose to the S/A region between 40-42Gy in 13 fractions being comparably safe as 25x 2.0Gy to 50Gy.

Keywords: BPN; Brachial plexus tolerance; Hypo fractionation; Radiation-induced brachial plexus neuropathy; Radiation tolerance

Introduction

The use of hypo fractionated irradiation of the whole breast has regained much interest after the publication of the results of large randomized trials showing equivalent results as when using standard fractionation (START A and START B, Canadian trial, randomized pilot trial for the START trial [1-6]. Based on these results from >7000 patients, the national institute for health and clinical excellence (NICE) has included the hypo fractionated regime with 40Gy/3 weeks in 15 fractions into its national guidelines [7], (http://www.nice.org.uk).

Some centers use hypo fractionation since many years, resulting in a large, albeit retrospective experience with these regimes [8-11].

History of the use of hypo fractionated radiation schedules for the breast at our institution.

During the period between 1967 and 1977, two regimes were used at our centre for curative irradiation of the whole breast or the chest wall: 5x 2.0Gy per week to 50Gy (± boost to 60-66Gy), or -in most cases- 3x3.3Gy per week to 42.9Gy. For logistic reasons, hypo fractionation was preferred in nearly all ambulatory patients with curative postoperative (post-mastectomy and breast conserving surgery) irradiation for breast cancer. In that period, in most patients the regional lymph nodes have also been included in the elective treatment volume. Since the opening of our department decades ago, life-long follow up of all patients used to be the standard practice; therefore nearly all irradiated patients had regular physical check-ups in our department, however since approximately 1985, most patients were no longer followed by physical examination at our department but regularly contacted by phone and/or by collecting follow up information with help of questionnaires.

After the publication of the results of the large fractionation study of the British Institute of Radiology (BIR) in 1978 [12] (showing inferiority of hypo fractionation as compared to norm fractionation schedules), hypo fractionation has, as a consequence, been abandoned in the curative treatment setting at University Hospital Zurich (USZ).

In 1993, Olsen et al. reported a relatively high rate of lesions of the brachial plexus after standard irradiation with 50Gy [13]. Motivated by that publication, in 1994, we reviewed the medical charts of all our loco-regionally controlled breast cancer patients treated with curative postoperative hypo fractionated radiation between 1967 and 1977, with focus on late term tolerance of the brachial plexus following

3.3Gy per fraction to the axillary ± supraclavicular (A/S) lymph nodes. Our first evaluation of the here presented cohort back in 1994 included a physical examination with focus on BPN in 25/130 patients, with a mean follow up of 18 years (5-36) post radiation; 56 additional patients could be contacted for a detailed phone call interview specifically focusing signs and symptoms of substantial BPN. For the remaining 49 patients (loss of follow up or death), specific information was extracted by reviewing their records: in 89% of the cohort there was no clinical sign of brachial plexus alteration. 13 women (10%) treated with 13x 3.3Gy described subtle neurological symptoms like pain in the arm and mild hypaesthesia (starting ~1-17 years post treatment, mean time to appearance not exactly known as symptoms may have been mild and therefore not always recognized/indicated by patients), which were not clinically relevant (grade 1 BPN, see grading below); objectively, a mild subcutaneous induration of the irradiated region was observed in those women. Of importance in this context is the fact that most patients treated in that historic era had undergone Halsted radical mastectomy and radical axillary lymphonodectomy.

Pleasingly, only one mild subjective and objectively not limiting grade 2 brachial plexus neuropathy (BPN) in one of the clinically assessed patient treated with 13x 3.3Gy was seen at that time.

Aim of this work

Due to the relatively low number of patients treated with hypo fractionated radiotherapy to the S/A region [14-19], the question of the brachial plexus tolerance continues to be discussed. In December 2013, we performed an update of the above described hypofractionation cohort, at a mean/median follow up time of meanwhile 28.1/26.6 years (7.2-44.8), aiming to re-assess the late term tolerance of the brachial plexus.

Methods and Materials

Patients

In December 2013, an update of the above described cohort was performed motivated by the again increasing interest in hypo fractionated radiation schedules nowadays.

The medical records of the eligible 130 patients were still available and were reviewed, in order to assess the long term tolerance of the brachial plexus following our 1967 to 1977, predominantly used hypofractionation schedule with 13x (12-15x) 3.3Gy in 3 fractions per week to the breast and S/A lymph nodes, (Table 1).

Parameters	Hypofractionation Cohort
number of patients	130
treatment interval	1967-1977
mean ageat radiation (range)	54 (27-77) years
at first analysis, 1994	73 (50-97) years
at last analysis, 2011	76 (50-98) years
T stage pT1/2/3/4	28/58/10/4%
N stagepN+/pN0	43/57%
follow up (FU) time	
mean / median (range), in years:	
all	28.1 / 26.6 (7.2-43.6)
lost of FU cohort (death, moved; 33%)	18.7 / 18.2 (7.2-27) *
known dead of disease (DOD, 2%)	at 18.5 and 25.6 years
INED (33%)	30.8 / 29.5 (20-38.9)
ANED (63%)	27.1/23.7 (7.2-43.6)
ANED, still alive (06/2011, 15%)	39.6 / 40.6 (38.3-42.5)
6-10 years FU	7%
>10-20 years FU	28%
>20-30 years FU	59%
>30 years FU	6%
previous breast surgery	
(mostly radical) mastectomy	98%
breast conserving	2%
hypofractionation schedules, 3f/w	
[BEΔ2ΓΨ, α/β=2/α/β=3, 5φ/ω]	
13x 3.3Gy= 42.9Gy[56/54Gy]	124
12x 3.3Gy= 39.6Gy[52/50Gy]	2
15x 3.3Gy= 49.5Gy[66/62Gy]	2
14x 3.3Gy= 46.2Gy[61/58Gy]	1
14x 3.5Gy= 49.0Gy[68/64Gy]	1
allive with known disease	
at first analysis, 1994	0, 1
at last analysis, 2011	2, 5

Table 1: Characteristics of the assessed hypofractionation cohort (n=130).

* 3 patients were alive with disease when last time seen, all others ANED; Loss of follow up was in most patients due to emigration to other countries; ANED: Alive and No Evidence of Disease when last time seen; AD: Alive with Disease when last time seen; DOD: Died of Disease; INED: Inter-currently died, No Evidence of Disease

None of the historic patient cohort underwent chemotherapy, and breast conserving surgery was performed in only 2%. In all patients the A/S lymphatic pathway was included into the radiation volume. Exclusion criteria as defined for the first assessment in 1994 were: (a) follow up period information of <5 years, and/or (b) local or regional recurrence. Four (4/134) loco-regionally disease free patients were excluded due to a too short follow up time; all four patients had no signs of BPN at last contact. From all of the remaining 130 patients any follow up information (i.e. clinical examination at our institution and/or information by phone, letters, charts) was available; in 78% of the cohort regular physical examinations at our institution for >5 years was performed. Since approximately 1985, most patients were no longer regularly physically examined at our department, but were

annually contacted by phone and/or questionnaires during the first 10 years and thereafter biannually. In addition, follow up information of all patients used to be regularly collected based on follow up letters of, or phone calls to caring family doctors and gynaecologists.

Methods

Definition of the used grading for PBN: In 1994, the following grading system has been defined and was used since to assess BPN in our patients:

Grade 0: no symptoms

Grade 1: anamnestic mild arm pain or weakness, without impact on daily life, plus the following clinical symptoms: dysaesthesia, hypo-/areflexia

Grade 2: paresis, functionally nonlimiting (plus all grade 1 symptoms)

Grade 3: disabling paresis or paralysis, with consecutive limitations in daily life

Radiation techniques

The used hypofractionation schedules are shown in Table 1.

The estimated Biological Effective Dose (BED, = D (1+d/(α/β)) to the used hypofactionated schedules for normofractionation (2Gy/day, 5 fractions (f)/week) is calculated for an alpha/beta ratio of 2Gy and 3Gy for the brachial plexus.

The A/S region radiation therapy has been performed by opposing antero-posterior (ap-pa) fields with equal weight and a midline dose of 39-49Gy in 3 fractions/week. Matching between ap-pa A/S and oblique opposed breast tangential fields was performed using tilt gantry and table rotation to compensate for beam divergence of the cobalt 60 machine as used in that period. Calculation of midline dose was then performed by manual calculation using depth dose tables. Source skin distance was 55-90 cm (90 cm in most cases). An example of an old simulation film (1972) of a supraclavicular/axillary radiation field is shown in Figure 1.

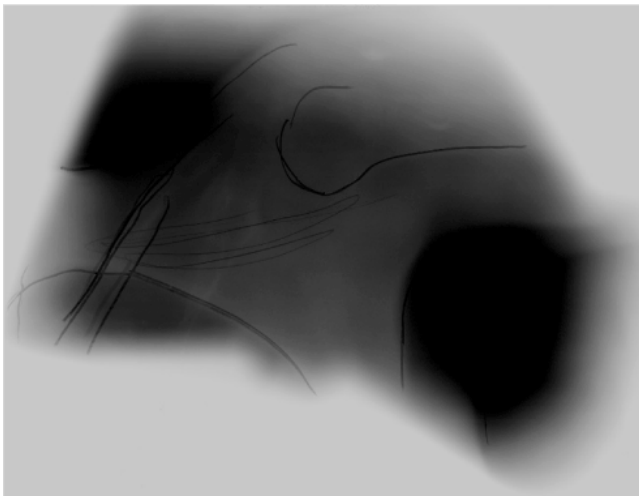

Figure 1: Simulation film of a supraclavicular/axillary radiation field (1972).

Two of the authors (KL and CG) performed recalculations of the dose distribution in 3 patients by using a CT calculation program for Cobalt 60. Recalculations were based on a model for a Siemens 'Gammatron R' cobalt unit (the machine that has been used for treatment of this patient cohort; model provided by Dr Richard Lösch, Klinikum St. Marien, Augsburg, Germany) in the Pinnacle [30] version 8.0 treatment planning system (TPS, Philips Healthcare, Andover MA).

Figure 2 shows dose distributions to the brachial plexus using different set ups as resulting from these recalculations; Figure 3 shows related dose volume histograms (DVHs) of the arm plexus using different treatment set ups (a-d).

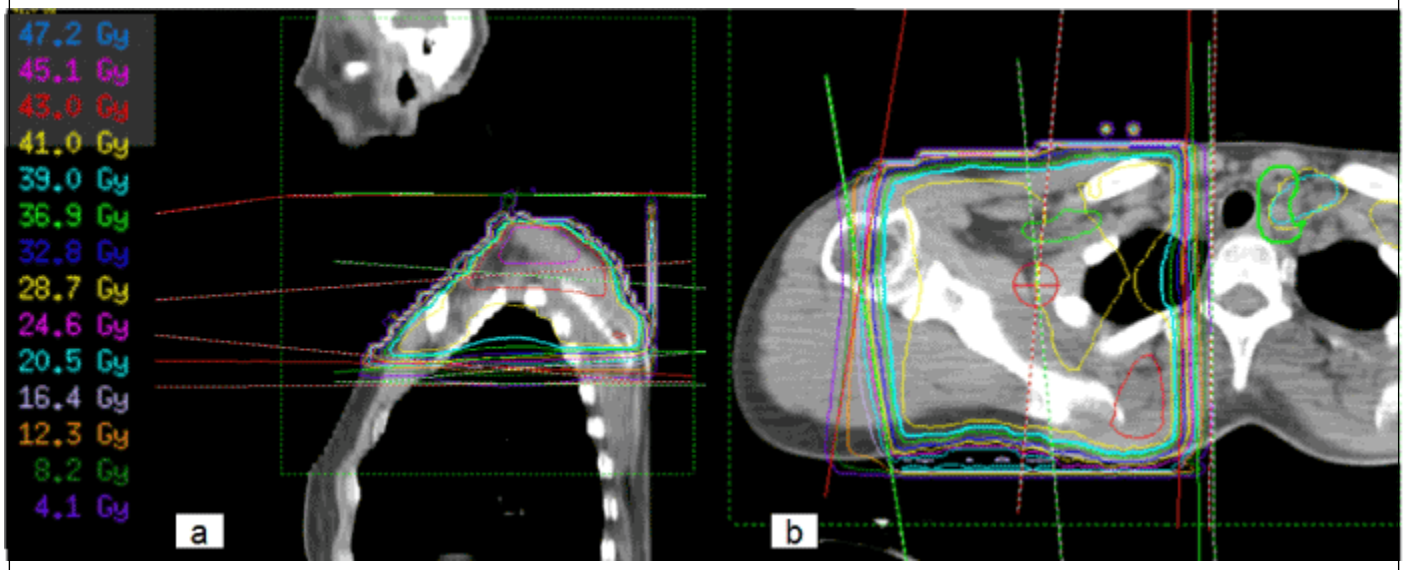

Figure 2: Dose distribution. **a)** Sagittal view of the dose distribution of opposed 6MV fields (midline dose) with 100cm source –isocenter distance **b)** Axial view of the dose distribution of opposed 6MV fields (mid plane dose) with 100cm source –isocenter distance.

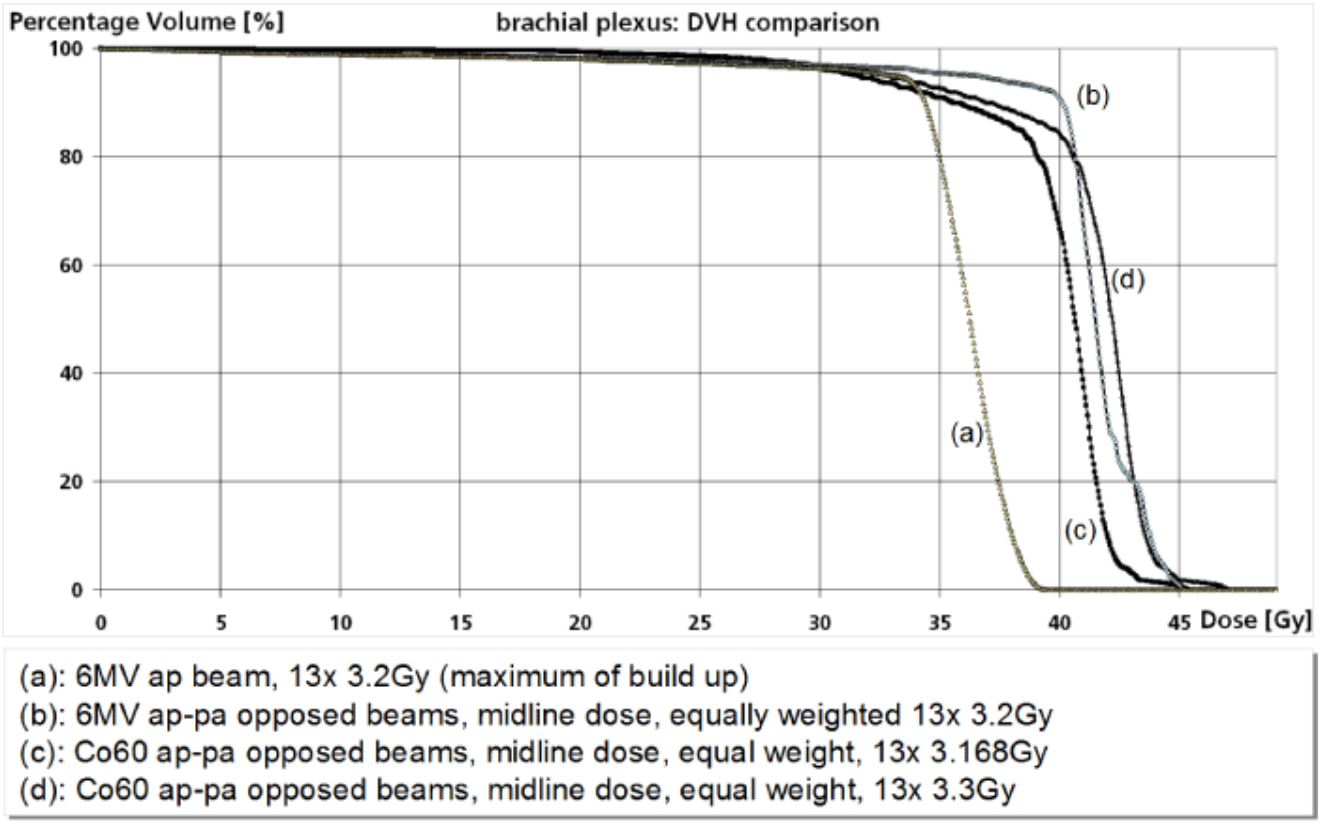

Figure 3: Dose Volume Histograms (DVH) of the arm plexus for different treatment set up, **a)** 6MV ap beam, 13x3.2Gy (max of build-up), **b)** 6MV ap-pa opposed beams, midline dose, equally weighted 13x3.2Gy, **c)** Co60 ap-pa opposed beams, midline dose, equally weighted 13x3.168Gy, **d)** Co60 ap-pa opposed beams, midline dose, equally weighted 13x3.3Gy.

Statistics

StatView® (Version 4.5) with its integrated calculation programwas used as data base andfor related calculation of follow up (no further statistics were calculated due to only one event).

Results

Follow up characteristics of the assessed cohort are listed in Table 2 and Figure 4.

Follow Up (FU)	clinical FU at USZ	FU information from letters/charts/ calls	known death
years (y)	%	letters/charts/calls +/- clinical FU, %	%
<5y	22	0	0
>/=5y	78	100	16%
5-10y	19	7	0
>10-15y	23	9	0
>15-20y	15	19	2
>20-25y	9	35	2
>25-30y	10	24	5
>30y	2	6	7

Table 2: Follow up characteristics of the own cohort.

Partial hypaesthesia of the upper arm was a frequently seen symptom, but was also recorded in the charts of many patients who had no S/A radiation, and may be related to the substantially more radical operation techniques (Halsted) used in the past. A frequent finding was a fat atrophy in the shoulder region. In addition, in one patient a subtle weakness of the arm was described, which, however was not limiting in the daily routine work (grade 1, diagnosed >16 years post treatment).

No grade 3BPN events developed in our cohort with a mean observation time of 28 years.

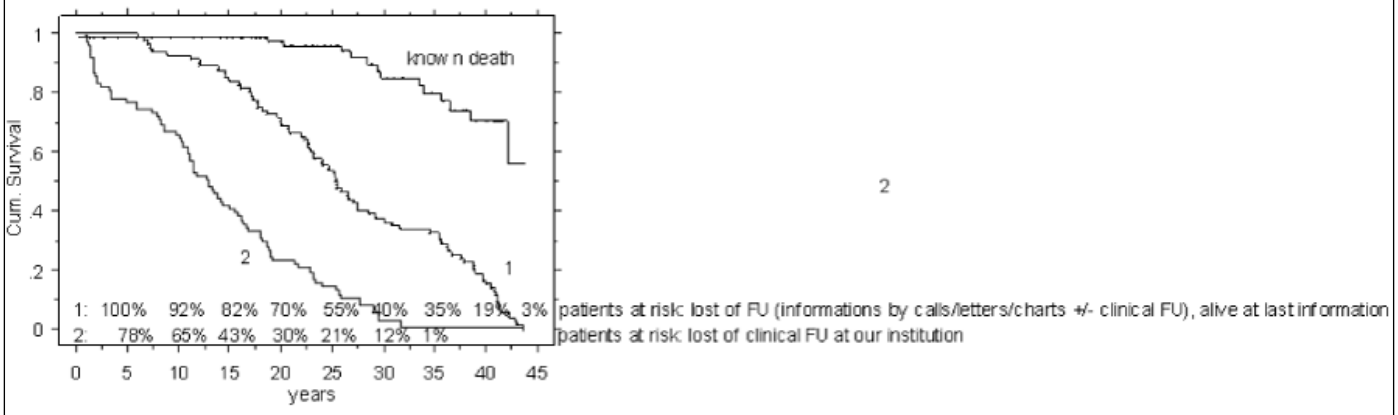

Figure 4: Kaplan Meier follow up curves analysed according to patients followed by information from charts, letters, phone calls +/- clinical FU at our department (1), isolated depicture of the clinical follow up at our department (2) and overall survival based on confirmed informationaboutpatients'death.

The above mentioned patient with grade 2 BPN as stated in1994 (see 'introduction'), was clinically examined for the last time in 11/2013,nearly 45 years after radiation therapy: this lady presents with a still persisting grade 1-2 BPN, no pain, being a content and active and indicating no additional complaints. Her history was the following: in the age of 40 this patient underwent breast conserving surgery for a T1N0 breast tumor in 1969, followed by hypo fractionated radiation with 13x 3.3Gy to the residual breast and the axillary region uses an ap-pa field technique, and to the supraclavicular region using an anterior field (calculated to 3cm depth). The arm plexus was most likely in the region of this field overlap. In 1983, 14 years later, the patient experienced a local recurrence of her disease and underwent a mastectomy and axillary revision. Grade 2 PBN with some degree of paresis of the arm was diagnosed in 1994. The patient kept on being able to work as a secretary performing mostly typing duties. As this activity requires substantial fine motor skills, the lesion was then classified asa grade 2 BPN.

Discussion

The aim of this work was to assess long term high grade BPN following hypo fractionated radiation to the arm plexus.

No grade 3/4 PBN was observed in the assessed cohort of patients treated with hypo fractionated radiation therapy using 3.3Gy in mostly 13 fractions.

The weakness of the study is its retrospective approach, and the lack of a specific investigation questionnaire regarding the brachial plexus function in order to detect milder BPN symptoms. More subtle degrees of BPN may have been missed by this method, although probably of limited relevance in daily life, and difficult to clinically differentiate from possible long term sequels after radical mastectomy, as performed in most patients of this historic cohort. Of importance to note in this context is that neuropathic shoulder arm symptoms and/or signs are common following mastectomy (±chemotherapy) only: in a prospective study on 100 surgery-only patients (50 patients

with modified radical mastectomy, 50 patients with wide local excision and axillary clearance treated between 2004-2006), 60% of patients reported one or more symptoms: numbness and pain in 39% each [20]. Arm symptoms were also reported most commonly during the first year after surgery ±radiotherapy to the breast by Liljegren et al in their randomized trial on 381 patients, and a further reduction was noted over the subsequent years by around 40-50% [21]. In the randomized ALMANAC trial >28% of 405 patients reported at least one arm symptom by 18 months post axillary surgery [22]. Engel et al. assessed 5-year quality of life data of 1131 patients in a prospective cohort study and found new and remained arm problems in 6% and 34% at year 4-5, respectively [23].

In the large Manchester analysis of >2000 cases treated with 40Gy/15fractions in 3 weeks, the same methodology was used to assess the follow up information (review of the case notes of all patients/contacting GPs and/or surgeons for information on patients who had been lost to follow-up or discharged) [24].

The focus of our analysis was on clinically relevant BPN (grade ≥ 2), which is hardly to miss by patients and caring physicians. Grade >/=2 symptoms are expected to be spontaneously reported by patients and related symptoms are evident at regular physical check-up, thus the presented study results are considered reliable.

The strength of the analysis lays in its long follow up time period of a relatively large sample size of patients treated with a homogeneous radiation regimen applied during one decade in a single institution, as well as in the regular clinical long term follow up at the same department (Table 1).

Regarding the BPN scoring, there is, to our knowledge, no specific standard available. Olsen et al. [13] defined a three-step grading, with 'disabling BPN in daily life' as grade 1: presence of disabling sensory disturbances, weakness, atrophy or hypoactivity of muscle stretch reflexes), 'mild BPN' as grade 2: all of grade 1, but mild), and grade 3: no BPN (absence of neurological signs and symptoms). Bajrovic et al. graded BPN using a modified LENT-SOMA four-step score [24], while we grouped symptoms to a three-step scale with emphasis on the functional aspect (see 'methods'); our grade 3 compares to the grades 3 and 4 in Bajrovic et al. and Olsen et al. grade 1, respectively.

A few papers describe rare instances of plexus lesions after a dose of 50Gy with 2Gy/fraction or 45Gy with 2.25Gy/fraction. Listed in Table 3 are selected published data on the rate of brachial plexus neuropathy (BPN) following differently fractionated radiation therapy of the breast and axillary ± supraclavicular regionpublished in the literature [1-3,9,13,14,25-33], showing a low rate of high grade BPN, comparable as following normal-fractionation.

FRACTIONATION	Author [ref]	Year	Treatment Interval	Follow up years (range)	n pat	Dose/Session (Gy)	Total Dose (GY)	~BED2Gy α/β=2Gy/3Gy	% BPN [grade]	Interval to BPN mean (range)
	[33]	1996	1958-1962	na (na - 2.5)	33	4.58	55	90/83	73% [1-3]	0.5-2.5 y
					84	4.25	51	80/74	15% [1-3]	0.5-2 y
	[14]	1987	1980-1983	na (na - 7)	250	3.4	51	69/66	2.4% [1 and 3]	0.3-2 y
H	[31]	1990	1982-1984	na (3-5.5)	338	3	45	56/54	5.90%	(1-4 year)
	[9]	1995	1981-NA	median 8 (2-11)	113	2.67	40	47/46	0%	0
	[26]	1995	1981-NA	median 8 (1-11)	334	2.67	40	47/46	0%	0
Y	[32]	1997	1979-1986	median 12.5 (na)	164	2.19	35	37/36	0%	0
	[29]	2000	1963-1965	(na - 34)	71	4	44	66/62	63% [1-4]	4.2y (<1-19 y
	[24]	2000	1989-1992	alive: median 5.9 (na - 10)	1148	2.66	40	47/46	0%	0
P	[27]*	2002	1984-1999	(na - 10)	89	6	30	60/55	0% [2-4]	0
	[25]	2004	1980-1993	median 7.3 (2.5-18)	332	2.6	52	60/58	14% [1-4]	>/=G3: 0.8%/ y
	[1]	2008	1999-2002	median 5.1 (max. 8.0)	119	3.2	42	54/52	0.1%[1]	2y
O	[2]	2008	1999-2001	median 6 (max. 8.0)	74	2.67	40	47/46	0	0

	[3]	2013	1999-2002	median 9.3 (max. 12.4)	193	3.20 or 2.67	41.6/40	54/52;47/46	none mentioned	0
	own study	2014	1967-1977	median 26.6 (7-45.2)	124	3.3	43	56/54	1%[2]	25y
	[30]	1992	19968-1985	median 6.6 (<1-19)	1117	2	50	50	1.8% [1-2]	10 months (1.5-77)
N	[13]	1993	1982-1990	median 4	128	2		50	9%/5% [1/3	no latency
O	[31]	1990	1982-1984	(3-5.5)	111	1.8	54	51	1% [?]	(1-4 years)
R	[28]	1990	1977-1985	median 10	697	2	50	50	<1% [na]	na
M	[1]	2008	1999-2002	median 5.1 (max. 8.0)	309	2	50	50	0%	0
O	[2]	2008	1999-2001	median 6 (max. 8.0)	153	2	50	50	0%	0
	[3]	2013	1999-2002	median 9.3 (max. 12.4)	462	2	50	50	none mentioned	0

Table 3: Selected published data on the rate of brachial plexus neuropathy (BPN) following differently fractionated radiation therapy of the breast and axillary ±supraclavicular region.

*: postoperative axillary radiation after axillary melanoma metastasis dissection, 2 fractions/week.

START A/B: no information available regarding axillary vs. supraclavicular vs. axillary and supraclavicular treatment volumes.

According to an analysis included in the protocol of the START A trial, at least in some of those patients the dose per fraction, the total dose and the dose to the plexus were higher than the prescription dose. This was also the case in our patient who developed grade 2 PBN (see 'method'). With the same relevance is the published decade long experience of supraclavicular and axillary irradiation with 40Gy in 15 fractions [24].

For our historic group radiated with 3.3Gy to the midline dose in 13 fractions, we re-calculated the dose distribution based on the planning CT of actual patients treated for breast cancer (Figures 2 and 3), the range of DVHs in this historic cobalt group includes very well the DVH of an equally weighted photon 6MV opposed field applying the dose of 13 fractions with 3.2Gy used in one of the arms of the START A trial.

Considering published results on the incidence and risk of various radiation regimes for brachial plexus lesions–including own results-, we come to the following conclusions:

The results from our historic group corroborate that a hypo fractionated regime as used in the START A and B trials as well as in the related pilot trials, and not exceeding the dose limits as listed in the START protocol (START A Trial Final Protocol; Standardisation of Breast Radiotherapy, July 1998 [13,30]), is as safe as applying 25 fractions with 2.0Gy target dose.

The results from our historic group corroborate the results in the START protocol (START A Trial Final Protocol; Standardisation of Breast Radiotherapy, July 1998): 'It seems reasonable to assume that an absorbed dose equivalent to 50Gy in 2Gy fractions at the level of the brachial plexus is safe in the absence of axillary surgery or chemotherapy. 'Safe' means a risk of radiation-induced BPN much lower (<1%) than the risk of malignant BPN were no radiotherapy to be given'.

The results of the Christie Hospital in Manchester based on >2000 patients [24] treated with a regime of between 40 and 42Gy in 15 or 16 fractions also supports this conclusion.

Conclusion

The long term follow up in our patients corroborates the hypothesis of a total mid plane dose in the supraclavicular/axillary region between 40-42Gy in 13 fractions being comparably safe as the normo fractionated regimen using 25x 2.0Gy to 50Gy.

Acknowledgement

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