6 Lack of radiation optic neuropathy in 72 patients treated for pituitary adenoma

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Journal of Neuro-Ophthalmology 2004; 24(3): 200-205

Abstract

The incidence of radiation optic neuropathy (RON) after external photon beam radiation therapy for non-functioning pituitary adenoma (NFA) is not well studied. Retrospective review was performed of ophthalmological and imaging data in 72 patients with NFA treated between 1985 and 1998 with external beam radiation therapy following surgery. Clinical follow-up after radiation therapy had to be at least 18 months. RON was defined as a sudden and profound irreversible visual loss affecting the optic nerve or chiasm. A review of previously published cases of RON was then performed. In our cohort, no patient had RON. A total of 11 adequately documented series reports of RON were found in the medical literature on radiation-treated NFAs. The incidence of RON in NFA from these series is 0.53% (95%CI, 0.26%-0.96%). An additional 14 single RON cases have been reported, bringing the total of adequately documented RON cases to 25. RON is a rare complication after external beam radiation therapy for NFA.

Introduction

Pituitary adenomas account for at least 12% of all intracranial neoplasms[1]. Their incidence is estimated to be 20 to 30 per million[2]. Approximately 25% to 30% of patients with pituitary adenomas do not have a classic hypersecretory syndrome such as acromegaly, Cushing disease, or prolactinoma. Tumors that do not appear to secrete hormones are called nonfunctioning adenomas (NFA)[3]. NFAs often present with signs of mass effect, such as visual changes, and symptoms of pituitary insufficiency[4].

Radiation therapy plays an important role in the treatment of NFAs. In the past, radiation therapy alone was the treatment of choice unless there were large visual deficits, in which case a craniotomy was performed to decompress the optic nerves and chiasm. With improving microsurgical techniques, the preferred treatment became neurosurgery followed by radiation therapy for extensive bulky lesions, histologically invasive adenomas, or incomplete excision[5]. The routine use of post-operative radiation therapy in case of residual tumor is controversial[6-9]; its use prevents regrowth of residual tumor in most cases, but it may cause such side effects as radiation optic neuropathy (RON)[10,11]. The incidence of RON after external beam radiation therapy for NFA has not been well-documented. There is also debate as to whether patients with NFA are less likely to have RON development after radiation therapy than those with growth hormone-secreting or adrenocorticotropic hormone-secreting pituitary adenoma[12-17].

The aim of this retrospective study was to discover the incidence of RON in a cohort of irradiated patients with NFA. Also, a review of prior published series and individual case reports is presented, from which an estimation of the incidence of RON in irradiated NFA can be deduced.

Methods

In 2001, we conducted a retrospective investigation of the ophthalmological, neurosurgical, and radiation therapy records of 77 patients who had undergone surgery and external beam radiation treatment of NFA from 1985 to 1998 at the University Hospital, Groningen, The Netherlands (n = 52) and four regional institutions with equivalent radiation therapy protocols (n = 20).

The median age of our cohort at the start of radiation therapy was 52 years. The sex distribution was 41 males (57%) and 31 females (43%). All 72 patients were treated with a combination of surgery and radiation therapy. Sixty patients had one, ten patients had two, and one patient had four operations before radiation therapy. One patient had a second operation for tumor recurrence after operation and radiation therapy. Median ophthalmological follow-up time after radiation therapy was 51 months (range, 19-171 months). Total radiation dose ranged from 45 to 55.8 Gy. The daily radiation fraction size

varied from 1.8 to 2 Gy. Median overall treatment time was 35 days (range, 30-42 days). The radiation fractionation schemes used were 45 Gy in 25 daily fractions (n = 49; 68%), 50 Gy in 25 daily fractions (n = 9; 13%), 50.4 Gy in 28 daily fractions (n = 7; 10%), 46 Gy in 23 daily fractions (n = 6; 8%) and 55.8 Gy in 31 daily fractions (n = 1; 1%). All radiation treatment fields were applied daily.

Patients were treated with linear accelerators with 4-MV photons (n = 5), 6-MV photons (n = 45), 8-MV photons (n = 11), 10-MV photons (n = 5), and 16 to 18 MV photons (n = 6). A two-field opposed lateral technique was used in 10 patients, a three-field technique in 30 patients, a five-field technique in 20 patients, and a combination of these techniques in 22 patients. The most frequent combination was opposed lateral fields, followed by a three-field (n = 13) or a five-field technique (n = 5). In the time period 1985 to 1990, the radiation dose to the tumor was prescribed at the tumor encompassing isodose, and from 1991 to 1998 it was prescribed at a central point in the tumor according to the recommendations of the International Commission on Radiation Units and Measurements (ICRU)[20].

Ophthalmological follow-up, defined as the period between the first day of irradiation and the last ophthalmological examination, had to be at least 18 months. Five patients were excluded because they were lost to follow-up before 18 months, reducing the cohort to 72.

Visual fields were obtained with Goldmann kinetic perimetry. The visual field data of all patients at diagnosis, after neurosurgery, radiation therapy, and in follow-up were reviewed by one neuro-ophthalmologist (J.-W.R.P.).

The diagnosis of RON was based on the criteria of Kline et al.[18] and Parsons et al.[19]; 1) irreversible visual loss with visual field defects of optic nerve or chiasmal origin; 2) absence of visual pathway compression caused by recurrence or progression of tumor, radiation-induced neoplasm, arachnoidal adhesions around the chiasm, radiation retinopathy, or other ophthalmologic disease; 3) absence of optic edema; 4) optic disc pallor noted within six to eight weeks after onset of symptoms. The diagnosis of RON was also based on review of visual fields, visual acuity, and fundoscopic examinations in combination with brain imaging.

For our review of the published literature on RON, we performed a search of Medline between 1966 and May 2003 and a search of Embase between 1989 and May 2003. Key words were radiation optic neuropathy, nonfunctioning pituitary adenoma, and radiotherapy. All articles that included patients with NFA were checked for vision loss caused by radiation therapy. The references retrieved by Medline and Embase were screened for other references not found using the aforementioned key words.

To estimate the incidence of RON in NFA, we included only cohort series of patients in which RON was studied. In reports that included functioning and nonfunctioning pituitary adenomas, we included only those in which the number of NFA and RON cases were reported. To evaluate risk factors for RON, we included only those cases from

series and case reports in which radiation treatment data were available. Our calculations include our own series as well as previous reports. The 95% confidence interval was calculated assuming a binomial distribution.

Results

In our cohort, no patient in the current study had RON diagnosed. One of 72 irradiated patients had spiraling isopters on Goldmann perimetry without visual acuity loss as late as 11 years after radiation therapy. Because of her unusual visual fields, Goldmann perimetry was repeated five times over a time period of 17 months with consistent spiraling. Fundoscopic examination of both eyes revealed normal optic discs. Gadolinium-enhanced magnetic resonance imaging showed no pertinent abnormalities, such as high signal in the optic nerves or chiasm[21]. Visual-evoked potentials showed no amplitude reduction or latency increase with pattern stimulation. Two years later, the spiraling had disappeared and visual acuity remained normal. Although she was initially considered to have atypical RON[22], this diagnosis was rejected when visual field defects normalized.

As shown in Table 1, we found 27 pertinent series of patients in whom the development of RON was considered. From these series, we calculated that 11 of 2,063 patients had RON, yielding an incidence of 0.53% (95% CI, 0.26%-0.96%). We found an additional 14 RON single-case reports in the literature, making a total of 25 cases.

In 16 of these cases, visual acuity loss was reported (Table 2). It was bilateral in nine patients (56%) and unilateral in seven patients (44%). Of the 25 eyes affected, 13 eyes (52%) had no light perception; two eyes (8%) had light perception; two eyes (8%) had hand movements; four eyes (16%) had a visual acuity between 20/800 and 20/100, and four eyes (16%) had a visual acuity better than 20/100.

In the 23 RON cases in which data were available, the peak latency between radiation therapy and the development of RON was between 12 and 18 months[18] (Table 2). The median latency time was 11 months (range, 2-54 months). Four patients (16%) had a latency period longer than 18 months.

In the 21 RON cases in which total radiation dose and radiation fraction size data were available, 14 patients (67%) received a total dose of more than 50 Gy and/or a daily fraction size more than 2 Gy. Of note, seven patients (33%) who had visual loss caused by RON were treated with a supposedly safe daily radiation fraction size and total radiation dose. Information was not available in most reports with respect to the ICRU 50/62 recommended minimum (95% of the prescribed dose) and maximum radiation doses (107% of the prescribed dose) to the optic system[20].

In the 20 RON cases in which patient age or gender was reported, the median patient age was 54 years (with 12 patients being older than 50 years), and 12 (60%) were women (95%CI,36%-81%).

Table 1 Incidence of radiation optic neuropathy (RON) in reported series of irradiated patients with nonfunctioning pituitary adenomas.

Ref	Number of patients	Total radiation dose (Gray)	Fraction size (Gray)	Number of RON cases	Treatment period
Colby, (1962)(27)	127	35	na	0	1938-1958
Emmanuel[28] (1966)	57	40	2	0	1940-1960
Chang[29] (1967)	291	24.5-30	2	0	1937-1964
Carlson[30] (1971)	38	31.6-58.5	na	0	1955-1965
Arumugasamy[31] (1971)	36	35-45	na	0	1942-1969
Hayes[32] (1971)	71	45-50	2	0	1950-1967
Pistenma[33] (1975)	62	44-70	na	0	1956-1972
Sheline[34] (1975)	140	40-50	na	0	1933-1968
Kramer[35] (1975)	143	45-46	2	0	1956-1972
Harris[24] (1976)	35	42-59	2-2.5	4	1968-1973
Aristizabal[12] (1977)	52	40-46	2-2.2	1	1952-1971
Erlichman[36] (1979)	154	17.2-55	na	0	1958-1972
Symon[37] (1979)	92	32.5-36	2.75-3	0	1968-1978
Ebersold[38] (1986)	50	40-57	na	0	1975-1980
Vlahovitch[39] (1988)	61	40-50	2-2.5	1	1968-1987
Flickinger[40] (1989)	112	47.5-50	2	1	1964-1987
Tran[41] (1991)	36	44-55	1.8-2.5	0	1967-1985
Grattan-Smith[42] (1992)	17	na	na	0	1980-1985
Salinger[43] (1992)	29	45.7-56	1-2.5	0	1961-1986
Zaugg[44] (1995)	35	40-45	1.8-2.25	0	1973-1992
Cornett[45] (1996)	8	45-60	1.8-2.0	0	1988-1992
Grabenbauer [46] (1996)	50	46-63	1.9-2.25	2	1983-1990
Colao[47] (1998)	59	45	1.8	1	1985-1996
Breen[48] (1998)	120	37.6-65.6	1.5-2.5	1	1960-1991
Mitsumori[49] (1998)	12	45	1.8	0	1989-1995
Sasaki[50] (2000)	65	44-70	1.5-2	0	1969-1994
Isobe[51] (2000)	39	48-60	2	0	1980-1995
Current series (2003)	72	45-55.8	1.8-2	0	1985-1998
Total	2063			11	

na: not available

Table 2 Reported cases of radiation optic neuropathy (RON) in irradiated patients with nonfunctioning pituitary adenomas in which radiation treatment characteristics are documented

Author (year of publication)	Gender	Age at RON (yrs)	Surgery	Total dose (Gy)	Fraction size (Gy)	Treatment time (days)	Latency of RON (months)	Visual status due to RON
Crompton, 1961(52)	F	56	Y	45	n.a.	28	12	n.a.
Harris[24*] 1976	F	41	N	45	2.25	32	6	OD: NLP; OS: 20/20
Harris[24*] 1976	M	62	Y	45	2.5	26	15	OD: NLP; OS: NLP
Harris[24*] 1976	M	66	N	45	2.5	26	6	OD: NLP; OS: NLP
Harris[24*] 1976	F	37	N	45	2.5	26	2	n.a.
Aristizabal[12*] 1977	n.a.	n.a.	n.a.	50	2	35	10	OD: NLP; OS: NLP
Martins[53] 1977	F	61	Y	67	2.25	37	33	OD: LP; OS: 20/20
Martins[53] 1977	F	44	Y	65.8	2.2	46	13	OD: NLP; OS: 20/30
Lorenzo[54] 1978	F	28	N	50	n.a.	35	14	n.a.
Fitzgerald[22] 1981	F	65	N	50	n.a.	42	13	OD: 20/20; OS: LP (helical isopters)
Fukamachi[55] 1982	F	49	Y	50	2	35	10	OD:20/400; OS:20/100
Hammer[15] 1983	F	52	Y	42.5	2.8	21	13; 25	OS: 20/200; OD: NLP
Kline[18] 1985	M	73	Y	50	2	38	12	OD: VA: 20/800; OS: 20/20
Kundra[56] 1990	M	40	Y	55	2.75	n.a.	6	n.a.
Kundra[56] 1990	M	46	Y	55	2.2	n.a.	+6	n.a.
Zimmerman[57] 1990	M	64	Y	50.4	1.8	28	14	OD:HM; OS:20/25
Millar[58] 1991	F	56	Y	45	1.8	35	10	OD: NLP; OS: NLP
Guy[21] 1991	M	51	Y	53.4	2	NA	30	OD: 20/20; OS: 20/25
Hudgins[59] 1992	F	75	Y	54	1.8	NA	35	OD: N/A; OS: 20/20
Sallet[60] 1992	F	40	Y	30	n.a.	n.a.	8	OD: 20/20; OS: NLP
Hughes[61] 1993	n.a.	n.a.	n.a.	50	2.5	n.a.	n.a.	n.a.
Hughes[61] 1993	n.a.	n.a.	n.a.	50	2.5	n.a.	n.a.	OD: 20/20; OS: 20/20, temporal field defect
McClellan[62] 1995	M	67	Y	45	1.8	36	3; 7	OD: HM; OS: NLP
Colao[47*] 1998	n.a.	n.a.	Y	45	1.8	35	12	n.a.
Breen[48*] 1998	n.a.	n.a.	n.a.	50	2	n.a.	54	n.a.

F: female; M: male; Surgery: Y: yes; N: no; OD: right eye; OS: left eye; VA: visual acuity; n.a.: data not available
* These references are also included in Table 1, because patient and treatment characteristics were available.

Discussion

Based on the review of our cohort of 72 cases and the published literature, RON is a rare complication after external beam radiation therapy in patients with NFA. We found no case of RON in our cohort. Our literature review found a total of 11 adequately documented cases of RON in series reports of radiation-treated NFA patients for an overall incidence of 0.53%. This is significantly lower than the 1.36% incidence of RON in acromegalic patients[23] ($P = 0.01$; odds ratio 2.56; 95% CI, 1.26-5.22). One possible determinant contributing to the relatively increased incidence of RON in GH-secreting pituitary adenomas compared to NFAs is the occurrence of more microvascular damage in association with GH excess[12].

An additional 14 RON cases emerged from single case reports. Reviewing the total of 25 cases, we found that RON usually occurred between 12 and 18 months after radiation treatment but could occur after a considerably longer latency period. Previous reports do indicate that a total radiation dose greater than 50 Gy and/or a daily radiation fraction size greater than 2 Gy are risk factors for developing RON[19,24], although RON can occur at lower doses[14,19].

In as many as 33% of reported cases, we could identify no risk factors related to radiation therapy. Older age has been touted as a possible risk factor for RON[9,25], but our series suggests that age is not a strong risk factor for developing RON in NFA, given the median age of 52 years at the start of radiation therapy among our patients. Our review also found no major gender predominance for the development of RON.

Based on these results, the current dose-fractionation policy in our department is 45 Gy in 1.8 Gy fractions for all pituitary adenomas. According to McCollough et al.[26], there is no benefit in applying a higher total dose.

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