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Radiotherapy for Peyronie's Disease: A European survey

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Abstract

Background and purpose. Peyronie's Disease (PD) is a benign condition characterized by penile nodules, pain and curvature. Radiotherapy has been used for many years with positive outcomes, however all studies published were non-randomized or non-controlled. The purpose of this survey was to understand which treatment policy is followed in Europe before setting up a randomized trial. *Materials and methods.* A questionnaire was sent out to 908 European radiotherapy institutions, 402 questionnaires were sent back and filled out correctly (44.5%). The questionnaire consisted of different items, regarding number of patients referred, fraction dose, total dose and technique used, and eventually treatment outcome of clinical trials. *Results.* Seventy-three institutions irradiate PD (19%), 304 do not (81%). Reasons for not treating were insufficient referrals from urologists or no interest in treating benign diseases. The most common fraction dose is 2 (range 0.5–8) Gy and the total radiation dose 20 (range 3–30) Gy. Most of the institutions use electrons (n = 44) or orthovoltage (n = 32). Decreased pain is reported in about 80% of the cases, and side effects by eight institutions. *Conclusions.* So far, a large variation of treatment schedules for radiotherapy of PD has been detected in European countries. Although the results are good and side effects minimal, there is still a need to set up a European randomized trial to prospectively evaluate the efficacy of radiotherapy for PD.

For several decades, radiotherapy of benign diseases has been a common practice in European countries, because of the anti-inflammatory or antiproliferative effects of low-dose radiotherapy [1]. However, because of the risk of induction of secondary cancer [2], radiotherapy of benign disease has gradually decreased in many Western European countries and subsequently many indications have disappeared. This is also the case for Peyronie's Disease (PD). PD, or induratio penis plastica, was named after François Gigot de la Peyronie, a French surgeon. PD peaks in the mid-fifties, which coincides with an age-related loss of tissue elasticity. Clinical data and anatomical pathology suggest that a trauma represents the initiation factor in PD; a bleeding into the subtunical spaces leads to fibrin deposition, resulting in the formation of a plaque [3]. The presenting symptoms of PD are penile pain, penile curvature during erection, presence of a plaque or induration, and erectile dysfunction [4]. Many studies on PD have been performed, though there is still no cure for this benign disease.

In a survey on indication and treatment schedules for radiation of benign diseases, Leer et al. [5] found a large variation in indications and treatment schedules throughout the world. This paper stressed the necessity and the importance of clinical studies and trials to assess the efficacy of radiotherapy of benign disease and to clear understanding of any risk involved. In this survey [5], PD was treated in less than 30% of the institutes in Europe, and in 50% when considering only Central Europe (Germany, Austria and Switzerland).

Although radiotherapy for PD has been reported to decrease penile pain considerably [6], all these studies were retrospective and non-controlled. The only way to correctly evaluate the efficacy of radiotherapy for PD is to set up a randomized trial as it has been done in the case of Graves'orbithopathy [7].

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Table I. Non-treating Institutes (n = 304).

Type of institution	n	%	Reason	
University hospital	147	48	No referrals	138
Community hospital	108	36	No interest	125
Private practice	37	12	No clinical effect	11
Other	12	4	Probable complications	2
			Combination of reasons	28

Before setting up such a randomized trial in Europe, it was thought to be worthwhile to perform a survey in European countries to know about the actual clinical practice and long-term experience on radiation for PD of European institutions, to evaluate the radiation schedules used and to evaluate which sort of trial European institutions would like to perform.

Materials and methods

In the fall of 2004, a questionnaire was sent out to 908 radiotherapy institutes listed in the ESTRO directory. Five questionnaires were returned because of an incorrect address; 25 institutions indicated that they had received it inappropriately because they were not treating patients. Taking also into account a second mailing, two months later, 402 questionnaires were returned (44.5%); of those, 73 institutions reported to treat PD (19%), while 304 did not do so (81%).

Results

Non-treating institutes

See Table I for an overview. Most of these centers stated that they did not treat PD because of insufficient number of referrals or because they were not interested in treating non-oncological patients. Interestingly only two institutes reported not to treat PD because of the possible complications of radiotherapy. Major countries not treating PD were Italy, France, UK and Germany.

Treating institutes

Fifty-seven hospitals reported to treat yearly 1–40 patients (Table II) and some of them were doing so since 1963. These institutions reported to use a fraction dose in the range of 0.5–8 (mean 2.4) Gy. Most of them (n = 43) used a 2 Gy fraction dose. Total dose was in the range 3–30 (mean 17) Gy, most of them (n = 29) using a total dose of 20 Gy. Numbers of fractions per week varied from 1 to 5 (mean 4); most of the centers (n = 39) using 5 fractions/week. Thirty-two institutes used orthovoltage (50–300 KV), 3 photons (4 or 6 MV) and 44 electron beams (4–13 MeV). Two institutes used either LDR or HDR brachytherapy and another 2 cobalt units. Different institutions reported to use different techniques, i.e. both orthovoltage and electrons. Additional bolus was used by four of the 32 institutes using orthovolt, two of three institutes using photons and 19 of 44 using electrons. Thickness of bolus used was 5 or 10 mm. Most of the centers treated patients in the supine position (n = 68), four sitting and one center in standing position. Forty-six institutions used to shield the testicles, 19 both the testicles and the suprapubic region, eight did not use any shielding. Patients were followed-up by 32 centers (1–60 months), while the other 41 referred the patients back to the urologist. Forty-two centers did not evaluate their results, 31 reported on 1–1200 patients treated in the previous years. Pain decreased in 75–85% of cases, with both orthovoltage and electrons, with no statistically significant difference. Side effects (dermatitis) were reported by eight institutions with no statistically significant difference between the different radiation techniques used. Quality assurance was used by five institutions (all community hospitals) and only three used clinical scores to evaluate the patients during follow-up. Twenty institutes stated not to be interested in participating in a trial, 53 were interested; see Table III for an overview.

Discussion

Peyronie's Disease remains a somewhat mysterious condition, and therapeutic advances have not yet resulted in a reliable "cure" of the disease, rather than a stabilisation of symptoms. The understanding of the wound healing process may offer new treatment modalities in the (near) future. The beneficial

Table II. Treating Institutes (n = 73).

Type of institution	n	%	Reason		Number pts/year (mean)
University hospital	26	36	Enough referrals	16	1–40 (5)
Community hospital	32	44	Knowledge of treatment	2	1–10 (3)
Private practice	13	18	Proven effect	3	1–15 (4)
Other	2	2	No side effects	1	
			All of above	19	
			A combination of above	32	

Table III. Interest in performing a randomized trial.

No interest	20
Radiotherapy versus sham	3
Different total doses	9
Radiotherapy versus tamoxifen	2
Central registry	10
All of above	29

effects of radiotherapy in early stages can be attributed to the anti-inflammatory properties of radiation [1]. Low dose radiotherapy has been given as very effective and low risk treatment for different inflammatory processes [1,5]. Recent radiobiological experiments *in vitro* and *in vivo* identified mechanisms that may be related to these anti-inflammatory radiation effects such as modulation of the adhesion of white blood cells and induction of nitric oxide synthase [1]. In a review paper on PD [6], we indicated that radiotherapy for PD was reported with encouraging results already in 1939. In the 1960s and 1970s different papers were published confirming satisfactory results with x-ray therapy in up to 90% of the patients regarding the pain, and 66% regarding penile curvature, with doses ranging from 3 to 24 Gy [6]. In this paper, it was stressed that radiotherapy tends to hasten symptomatic, natural and spontaneous improvement and that it should be limited to patients with penile pain [6]. Also in the 1990s the positive results of radiotherapy for PD were confirmed with relief from pain in up to 84% of patients treated. The major criticism of all these studies is the lack of a randomized and controlled design. Furthermore, results were based upon subjective reports by the patients and interpreted by the physician. We published a retrospective analysis of 179 patients with PD treated by radiotherapy [8]. To our knowledge this was the first study with a high number of patients. Most patients were treated by orthovoltage x-rays (123 patients) in 9 fractions of 1.5 Gy, 3 fractions per week. Fifty-six patients were treated by electrons to a dose of 12 Gy, in 2 Gy per fraction. Penile pain was diminished or had disappeared in 83% of the patients, 23% reported also an improvement in penile curvature [8]. No toxicity was reported. We concluded that low-dose radiotherapy is a non-invasive, not expensive, outpatient procedure with a high symptomatic relief resulting in a high satisfaction rate and causing no morbidity [8].

In a previous survey of radiotherapy for benign diseases [5], PD was treated in less than 30% of the institutes in Europe, and in 50% in Central Europe (Germany, Austria and Switzerland).

This is the first extensive survey performed in Europe specifically addressing radiotherapy of PD. About half of the institutes to which the questionnaire has been sent replied. Most of the European countries do not treat PD, mostly because they are interested in treating only oncological patients or because of the insufficient referrals by urologists. Among the treating institutions, we can conclude that they consistently report good results and very few side effects, though there is a large variation in fraction dose, total dose, technique and positioning used. This is a reason why there is place to set up a randomized trial to correctly evaluate whether radiotherapy is effective to treat PD. It is of outmost importance to establish an effective dose concept and to treat these patients in a randomized trial. Thus a proposal is prepared for a clinical trial that compares low-dose radiotherapy (e.g. 12–20 Gy) with sham radiation. It is mandatory to evaluate these patients before treatment using a standardized questionnaire and to follow-up them for at least one year.

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