

European Collaborative Group on Prostate Brachytherapy: Preliminary Report in 1175 Patients

S. Langley^{a,*}, R. Laing^b, A. Henderson^a, S. Aaltomaa^c, V. Kataja^d, J.-E. Palmgren^d, F. Bladou^e, N. Salem^f, G. Serment^e, L. Nava^g, A. Losa^h, G. Guazzoni^h, F. Guedeaⁱ, F. Aguiló^j, J.F. Suarez^j

^aDepartment of Urology, St Luke's Cancer Centre, Royal Surrey County Hospital, Stirling Road, Guildford, Surrey GU2 5XX, UK

^bDepartment of Oncology, St Luke's Cancer Centre, Royal Surrey County Hospital, Stirling Road, Guildford, Surrey GU2 5XX, UK

^cDepartment of Urology, Kuopio University Hospital, Kuopio, Finland

^dDepartment of Oncology, Kuopio University Hospital, Kuopio, Finland

^eDepartment of Urology, Marseille University Hospital, Marseille, France

^fDepartment of Radiotherapy, Institut Paoli Calmettes, Marseille, France

^gDepartment of Urology, San Raffaele Scientific Foundation, Milano, Italy

^hDepartment of Urology, San Raffaele-Turro, Milan, Italy

ⁱDepartment of Radiotherapy, Catalan Institute of Oncology, Barcelona, Spain

^jDepartment of Urology, Hospital Universitari de Bellvitge, Barcelona, Spain

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Abstract

Objective: To establish a multi-centre database of a large number of patients treated with brachytherapy across Europe.

Methods: A total of 1175 patient files were registered in the database and the completeness of the data on these patients resulted in the majority being included in the analysis.

Results: The database of patients treated with brachytherapy across Europe indicates that optimal patient selection for this procedure has been made, both in terms of outcome and side-effects, which will be subject of future analyses. This should enable refinement of the treatment choice and administration as well as provide useful guidance to other centres that want to establish this procedure for their patients. It will also set the ground for prospective studies.

Conclusions: The established database indicates that brachytherapy as a treatment option for prostate cancer is well established in many centres.

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1. Introduction

Current therapeutic options for localised prostate cancer include radical prostatectomy, external beam radiotherapy or brachytherapy. As prostate cancer screening is currently less common in Europe than America differences in tumour characteristics and comorbidity, especially co-existent lower urinary tract symptoms (LUTS) will be reflected in the patients presenting with early prostate cancer. Prostate bra-

chytherapy has been performed in the US since 1986 and a 10-year biochemical progression free rate of 85% has been reported by the Seattle group [1] from a series of 634 patients. Another series reported by Grimm et al shows a 10-year disease free survival rate of 87% in a series of 125 well-selected patients [2]. With regard to morbidity associated with brachytherapy, 50–80% of patients experienced temporary acute irritative or obstructive urinary symptoms requiring drug treatment [3,4], which persisted in 12% of patients at 12 months and in 6% at 24 months [5]. Acute urinary retention (AUR) has been reported in 1–14% of patients [3,4,6] and urinary incontinence

* Corresponding author. Tel. +44 1483 575511; Fax: +44 1483 555848.
E-mail address: stephen.langley@dial.pipex.com (S. Langley).

in 1–6% of patients [7–9]. In contrast, the European experience lags behind by 5–10 years compared to the US with limited reports of outcomes and morbidity. Henderson et al. [10] report a rate for AUR of 9.3% in their series of 216 patients treated with brachytherapy, while catheterisation was required by 13% of patients post-implant in another series of 60 patients [11]. A series of 249 patients from The Netherlands experienced urinary side-effects, including AUR in four (2%) and urethral strictures in three (1%) [12].

The current initiative was set up to establish a large patient series on prostate brachytherapy from across Europe. Members of the Prostate Brachytherapy Collaborative Group originate from five European centres: France, Finland, Italy, Spain and the UK where both a Urologist and a Radiation Oncologist are involved in the application of brachytherapy, which appears to optimise the team approach. The establishment of this group will allow large sampling of data/information from a wide range of centres in Europe to clarify results with this form of treatment and to investigate further refinements of patient selection, treatment, etc. This approach contrasts with published results from the US, which generally rely on single centre data. An additional benefit of establishing this multi-disciplinary group is that prospective studies on prostate implants can be conducted, involving a unified approach to this treatment.

Reported in this paper is the methodology of setting up the database. To illustrate the outcomes of this task, the first results will focus on the demographics of patients treated with brachytherapy across European borders. Outcome and morbidity will be presented in later publications.

2. Materials and methods

The five centres included in this paper have acquired good experience of brachytherapy by treating over 100 patients and overcoming their learning curve. These centres were chosen because a cohesive working relationship had been forged between a Urologist and Radiation Oncologist. Prostate implants are currently conducted as a routine technique. Overall, the established groups used comparable techniques and have included their first patients to undergo implantation and consecutive patients thereafter encompassing both their learning experience as well as those treated later in their individual series. In addition, each centre was able to offer both radical prostatectomy and conformal beam radiotherapy as well as brachytherapy as treatment options for localised prostate cancer.

2.1. Patient selection

Data on patients treated during May 1998 and August 2003 with transperineal ultrasound guided low-dose rate permanent seed brachytherapy in five centres in Finland, France, Italy, Spain and the UK were collated and pooled retrospectively. This

included: age; pre-treatment PSA level; Gleason Score; disease stage (TNM 2002) [13]; prostate size; urodynamic data (Q_{max}); symptom score (International Prostate Symptom Score [IPSS]); and other adjuvant therapies used (hormonal, external beam radiotherapy [EBRT]); brachytherapy protocol employed; dosimetry; post-implant morbidity; and patient follow-up including time to biochemical failure. With regard to disease stage, patients with T1a and b or T2a and b disease were grouped together. This was appropriate as only a small minority (0.3%) of patients were diagnosed after TURP (staged as T1a/b) and some centres had recorded data using the 1997 TNM classification which does not separate patients with palpable disease occupying < or > 1/2 of one prostate lobe.

2.2. Brachytherapy protocol

The five centres followed a similar brachytherapy protocol i.e. volume study with ultrasound, computerised dosimetry planning and post-implant dosimetry. Nomograms were not used. The majority of patients received seed implants as monotherapy with high dose/low dose rate I^{125} (stranded seeds RAPID Strand™, Oncura, UK). Some early patients received loose palladium seeds. External beam irradiation and/or hormonal therapy was applied in patients who were at significant risk of extracapsular extension as determined by intermediate and high risk group classification. In addition, selected patients were administered hormonal therapy

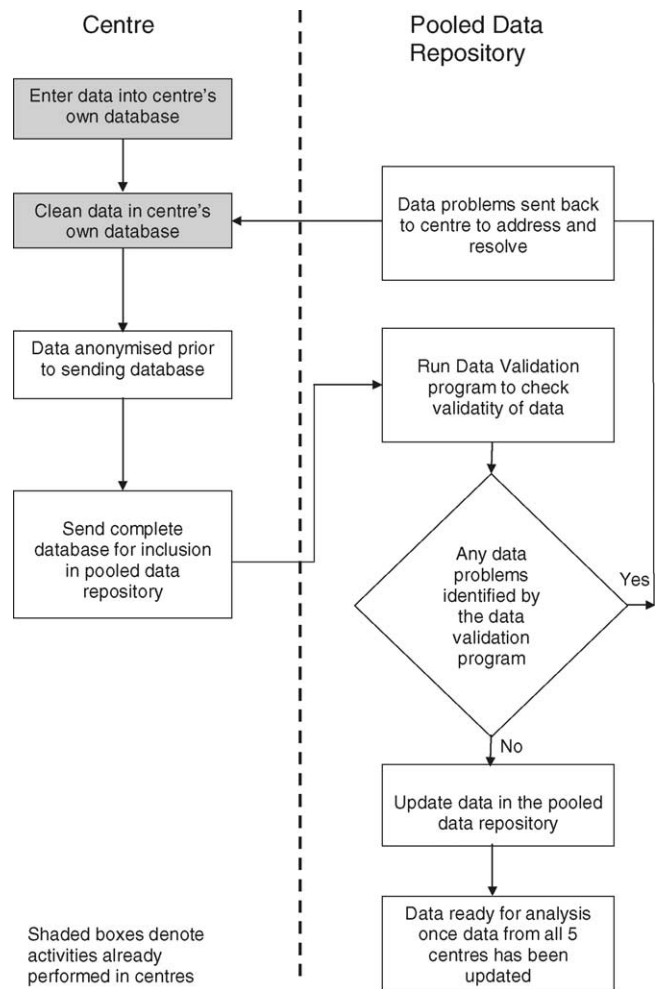


Fig. 1. Data collected and validation.

to reduce prostate size prior to implant or while curative treatment options were being determined.

2.3. Patient follow-up

Post-implant PSA levels were recorded at a minimum of 6-month intervals. Assessment of urinary morbidity was also noted using the IPSS questionnaires in the centres from Finland, Italy and the UK. Other complications, including urinary retention, transurethral resection of the prostate (TURP) incidence and incontinence, were variably recorded.

2.4. Data collection

Individual methods of data collection operated at the different centres. To rationalise this process and optimise capture, data from each country was collated according to the flow diagram shown in Fig. 1. Data validation was a crucial element of the process and any problems identified were returned to the centre inputting the information for clarification. On validation, data were entered into the pooled data repository. Analysis of predetermined variables took place when all values had been collated. All patients were anonymised at source.

3. Results

Data were collected on 1175 consecutive patients treated with brachytherapy during the specified period. Maximum follow-up time at present is 5 years.

3.1. Patient characteristics

Mean age at diagnosis across all countries was 64.7 (S.D. 6.6) years with ranges of 63.2 years in UK and

67.5 years in Italy where the age provided was the age at implant date (Table 1). Data from Finland, UK and Italy ($n = 617$) were collected on IPSS prior to implant and a median (range) value of 6.0 (0–29) points indicated that most patients had minimal pre-implant LUTS (defined as <8 points). The maximum flow rate (Q_{max}) is in keeping with such IPSS data and the mean of 18.8 (S.D. 8.7) ml/s suggests that few patients were likely to have experienced severe outflow tract obstruction (Table 1). Overall mean prostate volume was 33.8 ml (S.D. 11.4 ml) (Table 1), with means ranging from 30.9 ml (Spain) to 38.0 ml (Italy). PSA measurements on 1165 patients showed that mean (S.D.) level prior to implantation was 8.7 (4.9) ng/ml (Table 1). Data on prior surgery indicated that 20 patients had undergone a TURP (Table 1).

Prior hormonal therapy of any type was reported in 492 of 1175 patients (41.9%). The use of an antiandrogen was reported by France, UK and Finland for 270 of 860 (31.4%) patients and of a luteinising hormone-releasing hormone (LHRH) for 206 of 860 (24.0%) patients. EBRT was given to 118 patients, from France ($n = 9$), UK ($n = 79$) and Italy ($n = 31$) with unfavourable risk group prostate cancer.

3.2. Grade and stage

Gleason score and clinical stage are shown in Table 2. The majority of tumours were Gleason score 6 or below (86.8%) and stage T1c (49.5%) or T2a/b (36.2%).

Table 1
Patient demographics

		Spain	Finland	France	UK	Italy	Total
Total	<i>N</i>	150	174	327	359	165	1175
Age (years)	Mean	64.2	65.0	64.8	63.2	67.5	64.7
	S.D.	6.6	6.6	6.4	6.2	6.9	6.6
Pre treatment PSA (ng/ml)	Mean	6.5	10.1	9.3	8.7	8.2 ^a	8.7
	S.D.	2.1	6.5	5.4	4.1	4.8	4.9
IPSS	<i>N</i>	–	98	–	356	163	617
	Median	–	8.0	–	5.0	6.0	6.0
	Range	–	0–29	–	0–26	0–28	0–29
Q_{max} (ml/s)	<i>N</i>	–	158	–	314	163	630
	Mean	–	15.5	–	19.0	21.5	18.8
	S.D.	–	7.4	–	8.8	8.7	8.7
Prior surgery ^b	<i>N</i>	150	174	327	359	165	1175
	No	150	172	323	356	154	1155
	Yes	0 (0%)	2 (1.2%)	4 (1.2%)	3 (0.8%)	11 (6.7%)	20 (1.7%)
PV (ml)	<i>N</i>	123	173	316	355	100	1067
	Mean	30.9	33.5	31.4	36.1	38.0	33.8
	S.D.	9.3	12.7	8.4	13.0	10.9	11.4

PSA = prostate-specific antigen; IPSS = International Prostate Symptom Score; PV = prostate volume.

^a Data on 164 patients.

^b Transurethral resection of the prostate.

Table 2

Tumour grade and stage

Gleason Score	N	%	Tumour stage	N	%
ND	20	1.7	ND	2	0.2
2	17	1.5	T1a/b	3	0.3
3	59	5.0	T1c	582	49.5
4	197	16.8	T2a/b	426	36.2
5	241	20.5	T2c	141	12.0
6	505	43.0	T3a	21	1.8
7	114	9.7			
8	17	1.5			
9	4	0.3			
10	1	0.1			
Total	1175	100 ^a	Total	1175	100

ND = Not determined.

^a Total >100% due to rounding up.

3.3. Risk group analysis

Patients were categorised according into low-, intermediate- and high-risk groups according to pre-implant PSA, tumour grade and Gleason score (Table 3). The risk group system used was based on that established by the Seattle group [1]. The majority of patients fell into the low-risk category (58.0%) followed by intermediate risk (29.7%) and then high risk (10.1%). Data on 21 (1.8%) patients were insufficient to allow grouping.

4. Discussion

It has been possible to get the commitment of multi-disciplinary teams across Europe to participate in this collaboration, aimed at examining the European trend in cancer disease management in centres where all standard treatment options are available. This collaboration has produced the first pan-European multi-centre database of a large number of cases showing that brachytherapy is a treatment option well established in some centres. Demographic data on 1175 patients who underwent prostate brachytherapy have been collated and it is interesting to note considerable consistency in patient selection for the procedure, which is generally in line

with the recommendations of the ESTRO/EAU/EORTC [15]. Based on data from clinical trials, the ESTRO/EAU/EORTC guidelines recommend that patients with low volume localized disease (stages T1c–T2b) with a small risk of extra-capsular spread do well with brachytherapy alone [15]. With regard to tumour stage, the majority of patients treated were T2a/b or lower. It has also been established that patients with a Gleason 6 or less do well with brachytherapy alone [1,2]. Patients with Gleason 7 disease as a single risk factor (PSA <10 ng/ml; ≤T2b) also seem to have a good outcome from seed monotherapy [16,17]. Patients included in the current series were predominantly Gleason 6 or below. It is likely that tumours with a Gleason score of 2 were undergraded. Steinberg and colleagues from the Johns Hopkins Institute have reported on this phenomenon, with 78% of so-called Gleason 2–4 cancers graded by external pathologists being upgraded to Gleason 5–6 at their institute [18]. A study on interobserver reproducibility of Gleason grading demonstrated that 47% of Gleason score 5–6 were undergraded [19].

Pre-treatment PSA is one of the most significant prognostic factors for prostate cancer treatment. Patients with a PSA of less than 10 ng/ml tend to do well with brachytherapy alone, while those with a PSA greater than 20 ng/ml have an increased probability of biochemical failure [2]. The data collected in the current series indicate a mean PSA of 8.7 ng/ml, which is well within the optimal PSA level.

Risk groups for prostate brachytherapy have been established by a number of institutes and the most prominent of these come from groups in the US (Table 4). There are differences between the classification systems; for example, in the Seattle group classification [1], the intermediate group allows for more diversity of tumours with unlimited PSA, Gleason score or clinical stage than in the Mount Sinai [14] and D'Amico [20,21] classifications. This is relevant as one of the most controversial areas currently is whether patients with intermediate risk group disease should be treated by brachytherapy alone or in combination with EBRT. An RTOG study is addressing this issue, ran-

Table 3

Classification of patients according to Seattle risk group [1]

	Spain, N (%)	Finland, N (%)	France, N (%)	UK, N (%)	Italy, N (%)	All, N (%)
Low	136 (90.7)	84 (48.3)	181 (55.4)	174 (48.5)	106 (64.2)	681 (58.0)
Intermediate	14 (9.3)	57 (32.8)	104 (31.8)	128 (35.7)	46 (27.9)	349 (29.7)
High	0 (0)	17 (9.8)	41 (12.5)	57 (15.9)	9 (5.5)	124 (10.6)
Unknown	0 (0)	16 (9.2)	1 (0.3)	0 (0)	4 (2.4)	21 (1.8)
All	150 (100)	174 (100) ^a	327 (100)	359 (100) ^a	165 (100)	1175 (100) ^a

^a Total >100% due to rounding up.

Table 4

Risk group classification systems

Group	Low risk	Intermediate risk	High risk
Seattle risk group [1]	PSA \leq 10 ng/ml Gleason score 2–6 Stage T1–T2b	PSA > 10 ng/ml or Gleason score \geq 7 or Stage \geq T2c	Two or more risk factors: PSA >10 ng/ml Gleason score \geq 7 Stage \geq T2c
Mt Sinai risk group [14]	PSA \leq 10 ng/ml Gleason score <7 Stage <T2b	PSA 10.1–20 ng/ml Gleason score 7 Stage T2b	2 or 3 of the intermediate risk factors or PSA >20 ng/ml or Gleason score 8–10 or stage T2c–T3
D'Amico risk group [20,21]	PSA \leq 10 ng/ml Gleason score \leq 6 Stage T1c–T2a	PSA 10.1–20 ng/ml Gleason score 7 Stage T2b	PSA >20 ng/ml or Gleason score 8–10 or Stage T2c

domising patients with intermediate disease between the two different treatments. The majority of patients in the current series fell into the low risk group based on the Seattle classification.

Predictors of urinary morbidity following brachytherapy have been identified and include IPSS and prostate volume. Patients with an IPSS of less than 10 do well with a low risk of AUR and prolonged LUTS, while those with an IPSS score >20 have a 30–40% risk of these morbidities [22]. Patients with a prostate volume of 35 ml or less have a relatively low incidence of urinary morbidity and AUR compared with patients with higher volumes [5]. More recently it has been shown that the use of antiandrogens to downsize prostate volume prior to brachytherapy is associated with risk of AUR and a multivariate analysis in a group of 150 patients indicated that prostate volume and prior hormone use to be independent predictors of AUR [23]. The median IPSS score in patients from three countries (Finland, UK and Italy) was 6.0 points and mean prostate volume (all countries) was 33.8 ml, both suggesting, yet again, that optimal patient selection had been made and subsequent morbidity rate should be low.

Only 1.7% of patients included in the database had undergone prior prostate surgery. Recent TURP is a contraindication for brachytherapy as it is difficult to achieve a satisfactory seed distribution and in addition, these patients have a high risk of post-implant incontinence [7]. However, if TURP was performed several months previously and the prostate had largely regrown, patients can be considered for brachytherapy but steps must be taken to optimise dose distribution in order to reduce urethral dose.

Overall, 41.9% of patients had previously undergone hormonal therapy. In three countries, this comprised antiandrogen in 31.4% of patients and LHRH in 24.0%. Hormone therapy may be used in conjunction with radiotherapy for one of three reasons: to reduce pros-

tate size; to improve outcome of EBRT; and in the interim period before brachytherapy is applied. Although no randomized data are available, it seems that the efficacy of antiandrogens for prostate volume reduction is inferior to that of LHRH analogues and the role of antiandrogens prior to brachytherapy has yet to be established [24].

5. Conclusion

It has been possible to get the commitment of multidisciplinary teams across Europe to participate in this collaboration aimed at examining European trends in the management of prostate cancer by brachytherapy permanent seed implant. This collaboration has produced the first multi-centre database of a large number of cases showing that brachytherapy is a treatment option well established in some centres. Homogeneity of the data among centres has allowed the generation of a clear picture of what is happening with regards to brachytherapy in Europe. A total of 1175 patient files have been registered and the completeness of the data on these patients has resulted in the majority being included in the analysis. The database indicates that optimal patient selection for this procedure has been made. A retrospective analysis will be conducted of outcome and side-effects. This should enable refinement of the treatment choice and administration as well as provide useful information to other centres that want to establish this procedure for their patients. Follow-up and safety data will be the topic of future publications.

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Editorial Comment

T.M. de Reijke, *Amsterdam, Netherlands*
T.M.deReijke@amc.uva.nl

Brachytherapy using ¹²⁵I was first introduced in Europe, popularized in the USA and is now gaining again popularity in Europe during the past years. Unfortunately, a randomized study comparing radical prostatectomy, external beam radiation therapy and brachytherapy has never been done and will be very difficult to discuss with the patients. A randomized study comparing external beam radiation therapy and brachytherapy would also be of interest, especially since several modifications have been introduced for external beam radiation therapy, which could possibly enhance its efficacy and decrease its toxicity.

The authors are, however, to be complimented for this initiative to collect data on patients selected

for brachytherapy in Europe. If we look at the patient characteristics, they are all suitable candidates for either of the three treatment options with curative intent. It is, however, interesting to notice that almost half of the patients had (neo)adjuvant hormonal therapy. The only established reason for hormonal therapy in conjunction with brachytherapy is 'downsizing' of the prostate, it would thus be interesting to learn the reason for this high number of patients with hormonal therapy. Since we can expect a next publication with the safety and efficacy data, this high number of patients with hormonal therapy could be confusing for the interpretation of these data.

Finally, I think it is still a missed chance that only a selected number of centers have been approached for this collaboration, otherwise we could really have had a European database on brachytherapy.