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Published online: 13 Aug 2009.

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GEMMA GATTA[1], GIULIA ZIGON[1], ANTOINE BUEMI[2], JAN WILLEM COEBERGH[3], MARC COLONNA[4], PAOLO CONTIERO[5], LOUIS DENIS[6], PASCALE GROSCLAUDE[7], ANN VALÈRIE GUIZARD[8], MARIA JOSE SANCHEZ-PEREZ[9], IVAN PLESKO[10], MARTINA ONDRUSOVA[10], JADWIGA RACHTAN[11], RICCARDO VALDAGNI[12], MICHAEL VELTEN[13], MARINA VERCELLI[14] & FRANCO BERRINO[15]

[1]*Evaluative Epidemiology Unit, Fondazione IRCCS "Istituto Nazionale Tumori", Milan, Italy,* [2]*Haut-Rhin Cancer Registry, France,* [3]*Eindhoven Cancer Registry, The Netherlands,* [4]*Isère Cancer Registry, France,* [5]*Cancer Registry and Environmental Epidemiology Unit, Fondazione IRCCS, Istituto Nazionale Dei Tumori, Milan, Italy,* [6]*Oncology Centre Antwerp, Belgium,* [7]*Tarn Cancer Registry, France,* [8]*Calvados General Cancer Registry, France,* [9]*Granada Cancer Registry, Spain,* [10]*Slovakia Cancer Registry, Slovakia,* [11]*Cracow Cancer Registry, Cracow, Poland,* [12]*Direzione Scientifica, Prostate Program, Fondazione IRCCS "Istituto Nazionale Tumori", Milan, Italy,* [13]*Bas-Rhin Cancer Registry, France,* [14]*Liguria Cancer Registry, IST/Univ. Genova, Italy and* [15]*Department of Preventive & Predictive Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori*

Abstract

Background. There is wide variation in prostate cancer incidence and survival across Europe. In many countries incidence is rising sharply in relation to the introduction of prostate-specific antigen assay, and there is concern that patients may not be treated appropriately. We therefore aimed to characterize treatment for prostate cancer across Europe. *Methods.* We performed a high resolution population-based study, collecting information on the treatment of 3 486 prostate cancer cases diagnosed in 1995–1999 in 11 cancer registries from six European countries. *Results.* Overall, about one in three patients received radical treatment (prostatectomy 23% or radiotherapy 14%); about 60% of younger patients (<70 years) received radical treatment, while a similar proportion of older patients (≥70 years) received palliation (transurethral prostatectomy or hormone treatment only). A considerable proportion (61%) of patients with apparently high-risk disease were treated radically within a year of diagnosis, with large variation between regions: $>70\%$ in Calvados, Haut-Rhin, Tarn and Eindhoven and $<50\%$ in Slovakia and Cracow. Overall 34% of patients with apparently low-risk disease received radical treatment, varying from 17% and 22% in Bas-Rhin and Granada, to 52% and 56% in Calvados and Eindhoven. *Conclusions.* Our data indicate wide variation in the treatment for prostate cancer even among patients with apparently similar disease, and further suggest a non-negligible proportion may be receiving inappropriate radical treatment for apparently low-risk disease. Current guidelines indicate active surveillance should become the main means of managing low-risk disease.

In northern and western Europe and in many countries of central Europe, prostate cancer is the second most common cancer after non-melanoma skin cancer. Estimated annual incidence varies between 28/100 000 in eastern Europe and 80/100 000 in western Europe, while mortality rates are lower and differ less (12–20/100 000) [1]. Five-year survival for European men diagnosed with prostate cancer in the period 1990–1994 ranged from <40 to $>80\%$–a wider range than for any other cancer [1]. These wide ranges in survival and incidence are mainly attributable to differences in the intensity of opportunistic screening using prostate-specific antigen (PSA). Asymptomatic cancers diagnosed by PSA might be less aggressive than clinically detected cancers, but longer survival is probably mainly due to the prolonged lead time and length biases associated with very early detection [2].

As part of the EUROCARE project, we performed a population-based high-resolution study on prostate cancer, identifying cases from selected cancer registries (CRs) [3] and also obtaining clinical information on the procedures used to diagnose and treat the disease of individual patients. The aim of the

study was to characterize the treatments applied to this cancer across Europe at the end of the 1990s, and also to provide indications as whether treatments were appropriate. To do this we apply the criteria for the US SEER population based cancer registries [4].

Patients and methods

Eleven population-based CRs agreed to participate in the study and obtain high resolution clinical data not available in cancer registry databases: Slovakia, Cracow (Poland), Genova and Varese (Italy), Granada (Spain), Bas-Rhin, Calvados, Haut-Rhin, Isère and Tarn (France), and Eindhoven (The Netherlands) (Table I).

The CRs obtained detailed clinical information for cases of prostate cancer (ICD-9 185) [5] diagnosed in the period 1995–1999. The study protocol specified that at least 500 cases per CR were required and if this minimum was not reached in one year, the study period could be extended to obtain the required number. However, because of low numbers of incident cases, and for economic reasons related to obtaining detailed clinical information, less than 500 cases were frequently provided. Most CRs provided all cases incident in 1996–1998, with the exception of the French CRs, which provided random samples of about 200 cases from those diagnosed in 1995, and Eindhoven, which provided all cases incident in 1997–1999.

Cases notified by death certificate only (DCO) were excluded. Both histologically verified and non-verified cases were included. Details of the diagnostic and treatment procedures applied to each patient were obtained by consulting individual clinical records or clinical databases and abstracting the information onto a standard form. Extent of disease at diagnosis was classified according to the TNM classification [6]. Pathological T and N categories were used for patients undergoing surgery. When stage was not clearly stated, qualified CR personnel identified stage from clinical, imaging and pathological information present on patients' records. Tumour grade was categorized as: well, moderately, poorly differentiated, and unknown. Gleason score (GS) at diagnosis (range 2-10), grade at diagnosis (I, II, III), PSA (ng/ml) before treatment, and type of treatment as surgery [transurethral prostatectomy (TURP), radical prostatectomy or other specified surgery], radiotherapy or hormonal therapy (androgen deprivation, orchiectomy) were also abstracted. The results of three examinations (transrectal ultrasonography, abdominal CT, and bone scintigraphy) were recorded and used to reconstruct stage to serve as an independent check on stated stage. A total of 3 486 primary prostate cancer cases were analyzed.

For the purposes of this study we followed Miller et al. [4] and defined all therapies administered or planned within 12 months of diagnosis as *initial treatment*. A major aim of the study was to assess the type and frequency of initial treatment (surgery,

Table I. Prostate cancer cases by registry, year of diagnosis and age at diagnosis, with proportions of histologically verified cases and population covered by each registry (Source Globocan 2000 [1]).

Registry	Male population covered	No. of cases	Diagnosis period	Age ≥70 years (%)	HV* (%)
Slovakia	2609632	435	1996	62	98
Poland					
Cracow	349623	261	1996–1998	56	97
Spain					
Granada	395087	326	1996–1997	61	87
Italy					
Genova	439849	558	1996–1997	67	90
Varese	390267	608	1996–1997	60	93
France					
Bas-Rhin	483906	205	1995	56	98
Calvados	306095	199	1995	53	96
Haut-Rhin	341892	194	1995	63	99
Isère	525729	196	1995	62	98
Tarn	166692	197	1995	56	97
The Netherlands					
Eindhoven	487625	307	1997–1999	56	99
Overall		**3486**	**1995–1999**	**60**	**95**

*HV: histologically verified.

radiotherapy, hormone therapy, no treatment, or no information on treatment). Initial treatment was stratified by CR, age at diagnosis (<60, 60–69, 70–79, and ≥ 80 years), TNM stage (T1-4, N0, M0; any T, N+ M0; any T, any N, M+; and T1-2 localized or T3-4 advanced, N0, M0 when exact T was not available) and combined grade and GS (grade if GS unknown): well differentiated or GS 2-4; moderately differentiated or GS 5-7; poorly differentiated or GS 8-10).

To provide an indication of the appropriateness of treatment we analyzed the use of radical approaches (radical prostatectomy or radiotherapy) as initial treatment in relation to the risk class (high vs. low) of the cancer according to Miller et al. [4]. These authors [4] defined low risk prostate cancer as well-differentiated disease diagnosed at any age, or moderately differentiated disease diagnosed in men of 70 years or more. All other cancers were considered high risk. We excluded N and M+ cases at diagnosis from this analysis as they are not indicated for radical treatment. A modified Poisson regression model was used to estimate relative risks (RR) of being radically treated in a given CR region, adjusted by age, stage and tumour grade [7]. The analyses were performed with the Stata statistical package (Ver. 9.2) [8].

Results

Table I shows the distribution of cases by age and period of diagnosis, and the percentages of histologically verified cases. Sixty percent of patients were over 70 years of age, ranging from 53% (Calvados) to 67% (Genova); 95% of cases were histologically verified, range: 87% (Granada) to 99% (Eindhoven).

Table II gives a breakdown of initial treatments according to CR. About one in three patients received radical treatment (radical prostatectomy or radiotherapy), with prostatectomy performed more frequently than radiotherapy (22% vs. 14%). Twenty-one percent of cases received TURP; most of these cases are likely to have been discovered incidentally following pathological examination of tissue removed to treat prostate hyperplasia. Hormonal treatment alone was given to 31% of cases, while 10% received no therapy. Information on treatment was unavailable in 2% of cases: 6% in Granada and Genova, 4% in Isère, 1% in Slovakia, Varese, Bas-Rhin and Eindhoven, 0% in Cracow, Calvados, Haut-Rhin and Tarn (Table II).

Less than 30% of cases were treated radically in Slovakia, Cracow, Granada and Bas-Rhin, and in these CRs nearly half the patients received either hormonal treatment (Cracow, Granada) or TURP

(Slovakia, Isère). Thus, it is unsurprising that three of these registries (Slovakia, Cracow, Granada) had high proportions of metastatic (M+) cases at diagnosis (Table II).

As shown in Table III, about 60% of younger patients (<70 years) received radical treatments, while a similar proportion of older patients (≥ 70 years) received TURP or hormonal treatment. Slightly more than 50% of cases had localized disease (T1-2, N0, M0), and about 20% had distant metastases at presentation. Approximately 50% of patients with T2-3 disease underwent radical treatments, and as expected, hormonal therapy or TURP were given more often to M+ or to unknown stage cases. It is noteworthy that TURP as initial treatment was recorded in 54% of T1 cases: this treatment is usually given to patients with prostate hyperplasia in whom cancer is discovered subsequently. Half the patients with involved lymph nodes received radical prostatectomy. Tumour grade was available in about 85% of cases. Radical therapy was prescribed in 45% of moderately differentiated cancers, while more than half the patients with poorly differentiated disease received TURP or androgen suppression.

Table IV shows adjusted RRs of receiving radical treatment (prostatectomy or radiotherapy) according to CR, age, stage and grade. Age-, stage- and grade-adjusted RRs of receiving radical treatments were significantly higher than reference (Slovakia, with lowest proportion receiving radical treatment) in Genova, Varese, Calvados, Haut-Rhin and Tarn, and highest in Eindhoven. Age and stage differences explained most of the treatment differences between registries: the RR of receiving radical treatment decreased significantly with age. The RR of receiving radical treatment was significantly greater for T2, T3 and N+ cases, and much lower for M+ and unknown stage cases, than for T1 cases (reference).

Table V shows the percentages of patients who received radical treatments by CR, divided into low and high risk groups. Overall, radical treatments were given to 61% of high-risk and to 34% of low-risk cases. For all CRs except Slovakia, proportionately more high risk patients received radical treatment. More than 70% of high-risk cancers were treated radically in Haut-Rhin, Tarn and Eindhoven, and less than 25% of low-risk cancers received radical treatment in Granada and Bas-Rhin.

Table VI shows age-adjusted RRs of patients with low and high risk cancers receiving radical treatment. The age-adjusted RR of receiving radical treatment for low risk disease was significantly above the reference (Slovakia) for Eindhoven, and significantly below reference for Granada, and Bas-Rhin. The RR of receiving radical treatment for high risk

Table II. Prostate cancer cases according to cancer registry and initial therapy, and percentage of metastatic patients. Analysis performed on 3 486 cases.

Registry	Treatment						M+
	RP[1] %	RRT[2] %	TURP[3] %	Hormone only %	None %	Unknown %	%
Slovakia	19	4	43	23	10	1	43
Poland							
Cracow	13	14	10	48	15	0	32
Spain							
Granada	11	12	17	45	9	6	22
Italy							
Genova	25	14	11	33	11	6	12
Varese	35	3	12	34	15	1	10
France							
Bas-Rhin	16	11	35	27	10	1	17
Calvados	19	34	23	20	4	0	16
Haut-Rhin	17	24	19	31	9	0	26
Isère	16	15	45	18	2	4	13
Tarn	37	13	30	14	6	0	15
The Netherlands							
Eindhoven	19	36	12	25	7	1	12
Overall	**22**	**14**	**21**	**31**	**10**	**2**	**20**

[1]RP: radical prostatectomy; [2]RRT: radical radiotherapy; [3]TURP: transurethral resection; M+ =distant metastasis at presentation.

disease was above reference for all CRs. The risk difference was significant for all CRs except Cracow, Granada, and Isère. The RR of receiving radical treatment in patients with low risk cancer aged ≥70 years was significantly lower than reference (60–69 years). Among high risk patients of <60 years had a significant 20% higher risk of receiving radical treatment than those aged 60–69 years. By contrast,

Table III. Prostate cancer cases according to initial therapy, age, stage and tumor grade. Analysis performed on 3 407 cases (without cases with unknown treatment).

	N cases (%)	Treatment				
		RP[1] %	RRT[2] %	TURP[3] %	Only hormone %	None %
Age (years)						
<60	264 (8)	50	14	15	17	3
60-69	1102 (32)	38	18	18	21	5
70-79	1384 (41)	15	17	24	34	11
≥80	657 (19)	3	3	26	48	20
Stage						
T1	552 (16)	16	15	54	8	7
T2	1035 (30)	36	20	14	21	9
T1T2[†]	287 (8)	9	13	8	47	22
T3	416 (12)	34	19	17	26	4
T4	64 (2)	30	6	28	28	8
T3T4[¥]	66 (2)	9	3	5	71	12
N+	135 (4)	51	13	9	25	2
M+	673 (20)	4	8	21	54	13
Unknown	179 (5)	8	6	16	49	22
Grade						
Well diff.	847 (25)	20	15	32	24	9
Mod. Diff.	1583 (46)	30	15	18	29	8
Poorly diff.	498 (15)	17	16	25	36	6
Unknown	479 (14)	8	11	13	45	24
Overall	**3407 (100)**	**23**	**14**	**22**	**31**	**10**

[1]RP: radical prostatectomy; [2]RRT: radical radiotherapy; [3]TURP: transurethral resection. For cancers with exact T not available: [†]localized; [¥]advanced.

Table IV. Adjusted relative risks (RR) of radical therapy (radical prostatectomy or radical radiotherapy), with 95% CI, according to registry, age, stage and tumour grade.

	RR (95% CI)
Registry	
Slovakia	1
Cracow	0.92 (0.69–1.16)
Granada	0.99 (0.75–1.24)
Genova	**1.69 (1.36–2.01)**
Varese	**1.39 (1.12–1.65)**
Bas-Rhin	0.93 (0.69–1.17)
Calvados	**1.68 (1.33–2.03)**
Haut-Rhin	**1.41 (1.10–1.72)**
Isère	1.09 (0.83–1.36)
Tarn	**1.51 (1.20–1.83)**
Eindhoven	**1.72 (1.40–2.05)**
Age (years)	
<60	**1.18 (1.08–1.29)**
60-69	1
70-79	**0.63 (0.57–0.68)**
≥80	**0.14 (0.10–0.18)**
Stage	
T1	1
T2	**1.74 (1.51–1.97)**
T1-2[†]	**0.75 (0.57–0.94)**
T3	**1.58 (1.35–1.81)**
T4	1.15 (0.82–1.48)
T3-4[¥]	**0.42 (0.15–0.69)**
N+	**1.55 (1.27–1.83)**
M+	**0.48 (0.37–0.59)**
Unknown	**0.53 (0.33–0.72)**
Grade	
Well differentiated	1
Moderately differentiated	**1.21 (1.10–1.33)**
Poorly differentiated	1.07 (0.92–1.22)
Unknown	0.92 (0.75–1.09)

For cancers with exact T not available: [†]localized; [¥]advanced.

older age groups (≥70 years) had significantly lower risks of receiving radical treatment than reference.

Discussion

With regard to the first aim of our study–to characterize treatment for prostate cancer across Europe–our analysis shows that in the late 1990s, 37% of all prostate cancer patients received radical treatment for their disease in the regions studied. Furthermore, for high risk cancers, the RR of receiving radical treatment was about twice as high in Eindhoven, the Italian CRs and most French CRs, as in Slovakia (Table VI). The RR of receiving radical treatment correlated quite well with incidence (Pearson correlation coefficients $\rho = 0.59$ and $\rho = 0.61$ for radical treatment overall and for radical treatment in high risk cancer, respectively). In fact, annual incidence rates (Europe-standardized) were high (100–83 per 100 000) in all the French CRs and Eindhoven, intermediate (65–62 per 100 000) in the Italian CRs, and low (39–27 per 100 000) in Granada, Cracow and Slovakia [1]. High incidence could in part be due to extensive use of PSA testing, with a consequentially higher proportion of incident cases eligible for radical treatment.

Hormonal treatment alone (palliative treatment) was given to 31% of cases overall. As expected, hormonal treatment only was more often (48% or more) given to very old patients (80 years or more) and to M+ patients. Over 45% of patients in Cracow and Granada received hormonal treatment only. TURP must also be considered a palliative

Table V. Percentages of patients with low risk and high risk prostate cancer who received radical treatment (radical prostatectomy or radical radiotherapy) within a years of diagnosis by cancer registry (metastatic and N+ cases at diagnosis excluded).

Registry		No.	Low risk (%)[*]	High risk (%)[**]	Overall (%)
Slovakia		72	36	29	30
Poland	Cracow	62	34	44	36
Spain	Granada	63	22	58	26
Italy					
	Genova	183	36	56	39
	Varese	199	27	64	39
France					
	Bas-Rhin	52	17	59	32
	Calvados	92	52	73	61
	Haut-Rhin	63	38	79	47
	Isère	56	26	50	35
	Tarn	85	34	77	53
Netherlands	Eindhoven	165	56	75	63
Overall		**1092**	**34**	**61**	**41**

[*]Low risk: well differentiated plus moderately differentiated in patients ≥70 years old.
[**]High risk: moderately differentiated in patients <70 years, and poorly differentiated.

Table VI. Relative risks (RRs) with 95% CI of patients with low risk and high risk prostate cancers receiving radical treatment (radical prostatectomy or radical radiotherapy) by registry adjusted for age (metastatic and N+ cases at diagnosis excluded).

Registry		Low risk* (1 522cases)		High risk** (833 cases)	
		RR	95%CI	RR	96%CI
Slovakia		1		1	
Poland	Cracow	0.82	0.51–1.12	1.43	0.66–2.20
Spain	Granada	**0.62**	**0.40–0.85**	1.79	0.94–2.64
Italy					
	Genova	1.17	0.85–1.49	**1.98**	**1.15–2.81**
	Varese	0.82	0.59–1.06	**1.90**	**1.12–2.69**
France					
	Bas-Rhin	**0.55**	**0.28–0.82**	**1.94**	**1.10–2.77**
	Calvados	1.34	0.94–1.74	**2.39**	**1.38–3.41**
	Haut-Rhin	1.11	0.75–1.46	**2.58**	**1.54–3.63**
	Isère	0.93	0.55–1.30	1.80	0.99–2.61
	Tarn	1.10	0.70–1.50	**2.42**	**1.41–3.44**
Netherlands	Eindhoven	**1.52**	**1.13–1.92**	2.54	1.50–3.58
Age (years)	<60	1.24	0.98–1.51	**1.18**	**1.07–1.29**
	60-69	1		1	
	70-79	**0.69**	**0.59–0.79**	0.48	0.34–0.61
	≥80	**0.11**	**0.06–0.17**	**0.11**	**0.03–0.19**

*Low risk: well differentiated plus moderately differentiated in patients ≥70 years old.
**High risk: moderately differentiated in patients <70 years, and poorly differentiated.

treatment when given to M+ or T4 patients. In fact TURP was given to over 20% of M+ or T4 patients, and in Slovakia, with the highest proportion of M+ cases, 43% of all cases received TURP.

The second aim of our study was to provide an indication of the treatments given for prostate cancer in the second half of the 1990s. This is important since, following the introduction of extensive PSA testing, the incidence of prostate cancer has increased markedly [9,10] and there is concern that many patients may be overtreated, particularly older men. In fact European observational studies indicate that the natural history of expectantly managed localised prostate cancer, particularly among older men with clinically detected low- and moderate-grade tumours, is indolent [11–13]. Miller et al. [4], who examined care among US prostate cancer patients diagnosed in 2000–2002 and archived in the SEER population-based cancer database, found that the main problem was not whether potentially lethal cancers were adequately treated but that low-risk ones were being overtreated. Overtreatment implies increased risks for patients without conferring benefit, and is also costly.

We performed a similar analysis on the cases collected in this study. After Miller et al. [4] we defined overtreatment as use of radical approaches in men diagnosed with low-risk cancer. The Miller risk classification is appropriate for population-based analyses where not all clinical information is available for all cases. More detailed risk classifications [14,15] are intended for clinical use.

In the USA CR regions, 55% of low risk cancers received radical treatment, while in the European CRs, 34% of patients with apparently low-risk cancers received radical treatments within a year of diagnosis (Table V). However, in Eindhoven and Calvados, the proportions of overtreated patients were considerably higher, and approached the USA figure.

The appropriate initial approach for low-risk cancers should be expectant management [11–13,16] – an approach involving active surveillance with curative treatment delayed until it becomes necessary (if ever). This approach appears as an attractive solution to the problem of overtreatment in lower-risk prostate cancer. There is evidence that this strategy was being applied to modest extent in our cases: 25 patients with low-risk prostate cancer at diagnosis received radiotherapy (17 cases) or radical prostatectomy (8 cases) during the second and third years after diagnosis.

Like Miller at al. [4] we included GS 7 cancers among low-risk cases and this may have inflated our estimates of overtreatment, since these cancers have a greater risk of progression than GS ≤6 cancers [11]. We collected the PSA titres reported at first admission on the clinical records and performed a post hoc analysis of PSA levels finding that they were significantly higher (Kruskal Wallis test, p =0.01) in high risk than low risk cancers.

With regard to the limitations of the present study, biased results may arise from variations in data quality between CRs, and marked differences in

data quality would compromise comparability. Overall 2% of cases had missing data on treatment, however, this figure was higher in Granada (21 cases, 6%), Genova (35 cases, 6%) and Isère (7 cases, 4%). As expected, treatment information was lacking in 4% of patients aged 75 years or more, and in 16% of cases with unknown stage. These variations in treatment data quality are contained and seem unlikely to substantially bias our findings. Thus, assuming that all these unknown treatment cases were treated radically, this would change our findings only slightly: low risk patients receiving radical treatment change from 34 to 37% and high risk patients change from 61 to 63%. With regard to tumour grade, this was missing in 69 cases (6%) of radically treated cases (excluding N and M+ cases). Assuming that all these unknown grade cases were either all low-risk or either high-risk cases, would again change our findings to a small extent: low risk patients receiving radical treatment change from 34 to 37%; risk patients change from 61 to 64%.

To conclude, our population based-data from a fairly wide selection European CRs at the end of the 1990s indicated that about one in three of the prostate cancer patients we surveyed received radical treatment, with prostatectomy performed more often than radiotherapy. We also estimated that a considerable proportion (as high as 34%) of patients with apparently low-risk disease were treated radically within a year of diagnosis. This proportion is lower than estimated in the USA in 2000, although some European regions approached USA overtreatment levels. Since the incidence of prostate cancer will increase in the near future as PSA testing becomes even more widespread, the proportion of low-risk cancers diagnosed should also increase. Expectant management (active surveillance and delayed treatment) should become the main approach to low-risk disease. Monitoring the extent application of expectant management will be a useful way of assessing the appropriateness of treatment for this disease in the future.

Acknowledgements

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