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Platinum Priority – Infections

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Infective Complications After Prostate Biopsy: Outcome of the Global Prevalence Study of Infections in Urology (GPIU) 2010 and 2011, A Prospective Multinational Multicentre Prostate Biopsy Study

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Abstract

Background: Infection is a serious adverse effect of prostate biopsy (P-Bx), and recent reports suggest an increasing incidence.

Objective: The aim of this multinational multicentre study was to evaluate prospectively the incidence of infective complications after P-Bx and identify risk factors.

Design, setting, and participants: The study was performed as an adjunct to the Global Prevalence Study of Infections in Urology (GPIU) during 2010 and 2011. Men undergoing P-Bx in participating centres during the 2-wk period commencing on the GPIU study census day were eligible.

Outcome measurements and statistical analysis: Baseline data were collected and men were questioned regarding infective complications at 2 wk following their biopsy. The Fisher exact test, Student *t* test, Mann-Whitney *U* test, and multivariate regression analysis were used for data analysis.

Results and limitations: A total of 702 men from 84 GPIU participating centres worldwide were included. Antibiotic prophylaxis was administered prior to biopsy in 98.2% of men predominantly using a fluoroquinolone (92.5%). Outcome data were available for 521 men (74%). Symptomatic urinary tract infection (UTI) was seen in 27 men (5.2%), which was febrile in 18 (3.5%) and required hospitalisation in 16 (3.1%). Multivariate analysis did not identify any patient subgroups at a significantly higher risk of infection after P-Bx. Causative organisms were isolated in 10 cases (37%) with 6 resistant to fluoroquinolones. The small sample size per participating site and in compared with other studies may have limited the conclusions from our study.

Conclusions: Infective complications after transrectal P-Bx are important because of the associated patient morbidity. Despite antibiotic prophylaxis, 5% of men will experience

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an infective complication, but none of the possible factors we examined appeared to increase this risk. Our study confirms a high incidence of fluoroquinolone resistance in causative bacteria.

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1. Introduction

Prostate biopsy (P-Bx) is currently an essential procedure for prostate cancer diagnosis [1] and a frequently performed procedure in urology with an estimated 1 million cases each year in Europe. Following the introduction of transrectal ultrasound-guided P-Bx [2], this procedure has been widely accepted and optimised in recent years, continuously following the transrectal route [1]. A systematic review on randomised controlled studies (RCTs) on antibiotic prophylaxis in transrectal P-Bx showed a significant reduction in the risk of bacteriuria compared with placebo [3]. Reductions in symptomatic urinary tract infections (UTIs) and bacteremia were also seen but did not reach statistical significance [3]. Clinical guidelines therefore recommend antibiotic prophylaxis, typically with a oral fluoroquinolone, prior to transrectal P-Bx [4,5]. Several reports have recently suggested an increased rate of infective complications following transrectal P-Bx in both North America [6,7] and Europe [8]. The reasons for this increase and the factors associated with a higher susceptibility to infection remain largely unknown.

The aim of this international study was to evaluate the worldwide prevalence of infective complications after P-Bx and determine whether putative risk factors are associated with a higher rate of infection.

2. Material and methods

2.1. Study design

This prospective observational multinational multicentre epidemiologic study was performed as a part of the annual worldwide Global Prevalence Study on Infections in Urology (GPIU) in 2010 and 2011. The GPIU study has been performed annually since 2003 and consists of a 1-d prevalence census of infections experienced by patients hospitalised in urology units. It is organised by the board of the European Section for Infections in Urology (ESIU) [9,10]. The study was endorsed and sponsored by the European Association of Urology (EAU) and carried out in collaboration with several other medical societies (see acknowledgements). The GPIU study was approved by the ethics committee of Justus-Liebig-University, Giessen, Germany (ethical vote: AZ: 116/07). Obtaining regulatory approval was the responsibility of each study centre.

The aims of the GPIU prostate biopsy study were (1) to audit the prevalence of infective complications after P-Bx across centres and countries participating in the GPIU study and (2) to evaluate factors associated with a higher risk of infective complications.

All patients undergoing P-Bx during the 2-wk period commencing on the GPIU study census day in November 2010 and 2011 onwards were eligible to be included. Each included participant was required to be observed for 2 wk after biopsy either by onsite investigation or telephone interview.

2.2. Internet portal

The study was performed using the Internet-based platform Uroweb, the Internet portal of the EAU that provides all protocol details and uploading of results to a patient database. The software was developed (v.0.9) in PHP (a recursive acronym for PHP Hypertext Preprocessor). For the P-Bx study, investigators at participating sites completed online case report forms on a password-protected Web site with a site-specific login (<http://www.uroweb.org/>). These anonymised data were stored securely in a specially designed MySQL database [9,10].

2.3. Patient information

The case report form consisted of two parts. The first part included questions on patient characteristics (age, use of antibiotics in preceding 6 mo, history of urogenital infection in preceding 6 mo, prostate volume, prostate-specific antigen [PSA] value, previous biopsy) and the biopsy process (route, result of preoperative urine culture, performance and type of preoperative bowel preparation, performance and type of antibiotic prophylaxis, number of cores taken, performance of local anaesthesia). The second part comprised questions on the outcome of biopsy (presence of histopathologic inflammation, presence and severity of symptoms of UTI at any time up to 2 wk after biopsy, physician visit for UTI and type of visit, readmission to the hospital, results of urine culture and inflammatory markers, type of treatment antibiotic used, and final clinical outcome at follow-up date).

To assess factors for increased infective complications after P-Bx, patients with infective complications were compared with patients without infective complications with regard to possible adverse risk factors of increasing age, higher prostate volume, higher preoperative PSA level, past history of UTI, and prebiopsy bacteriuria in patients investigated with urine culture, preoperative bowel preparation, history of antibiotic pretreatment, performance of antibiotic prophylaxis, type of antibiotic prophylaxis, duration of antibiotic prophylaxis, repeated P-Bx, use of local anaesthesia at P-Bx, number of biopsy cores, and histopathologic presence of inflammation in the biopsies.

2.4. Statistics

Dichotomous variables were compared with the two-sided Fisher exact test and continuous variables with the two-sided unpaired Student *t* test or Mann-Whitney *U* test, where appropriate. A binary logistic regression analysis was used to examine the association between possible predictive factors for the occurrence of a UTI after P-Bx. Missing values were not imputed in the model. We did not include the variables prostate volume or presence of preoperative bacteriuria in the multivariate analytical model because they were recorded for less than half of the cohort. An α value of 0.05 was determined to be statistically significant. Statistical analyses were performed using PASW Statistics 20 for Windows (SPSS GmbH Software, Munich, Germany).

3. Results

A total of 84 centres in Africa ($n = 2$), Asia ($n = 11$), Europe ($n = 67$), and South-America ($n = 4$) participated in the GPIU prostate biopsy study (see appendix). The centres included

Table 1 – Evaluation of prostate biopsy performance in 702 men

Parameter	Patients, no. (%)
Urine examination prior to biopsy	418/702 (59.5)
- Reagent strip urinalysis	254/702 (36.2)
- Urine culture*	164/702 (23.4)
Antibiotic treatment for bacteriuria prior to biopsy	2/702 (0.3)
Lower bowel cleansing	297/702 (42.3)
- Enema	246/702 (35.0)
- Antiseptic lavage	25/702 (3.6)
- Other	26/702 (3.7)
Repeat set of biopsies†	151/702 (21.5)
Antibiotic prophylaxis‡	689/702 (98.2)
- Fluoroquinolone-based antibiotic prophylaxis	637/702 (90.8)
Transrectal prostate biopsy§	684/702 (97.4)
Transperineal prostate biopsy§	18/702 (2.6)

* Bacteriuria was found in 8 of 164 patients (4.9%): *Escherichia coli*, n = 2; *Klebsiella* species, n = 2; *Pseudomonas* species, n = 1; *Staphylococcus epidermidis*, n = 1; *Enterococcus* species, n = 1; *Candida parapsilosis*, n = 1.

† Second set, n = 106; third set, n = 31; fourth set, n = 7; fifth set, n = 3; seventh set, n = 2; unknown sequence, n = 2.

‡ Duration of antibiotic prophylaxis was a median of 3 d (range: 1–21; standard deviation [SD]: ±2.5).

§ A median of 12 biopsy cores (range: 1–40; SD: ±3.9) were obtained per patient.

a median of 4 evaluable patients for each year of participation (range: 1–25; standard deviation [SD]: ±6.7). A total of 702 men were included across the two study years (2010, n = 385; 2011, n = 317). Median patient age was 66 yr (range: 40–90; SD: ±8.0). Table 1 shows the biopsy performance parameters.

Outcome at 2 wk was available for 521 of 702 men (74.2%) (2010, n = 290; 2011, n = 231) (Table 2). Symptomatic UTIs were recorded in 27 of 521 patients (5.2%), with dysuria (n = 19), frequency (n = 18), urgency (n = 10), and prostate pain (n = 9) the most frequent symptoms. Urine culture was positive in 10 of 27 cases (*Escherichia coli*, n = 8; *Pseudomonas* species, n = 1; *Klebsiella* species, n = 1). Fluoroquinolone resistance was observed in 6 of 10 isolates. Febrile UTIs were present in 18 of 521 patients (3.5%), and 16 of 521 patients (3.1%) required hospitalisation due to

infection. This included one patient admitted to the intensive care unit with uroseptic shock 1 d after P-Bx. In two men the infection had not resolved by the end of the 2-wk follow-up period. A total of 494 of 521 men (94.8%) showed no evidence of infective complications at up to 2 wk after biopsy. Symptomatic UTI was reported in 1 of the 2 patients submitted by centres in Africa, 3 of 57 submissions (5.3%) from centres in Asia, 21 of 441 submissions (4.8%) from European centres, and 2 of 21 submission (9.5%) from centres in South America. There was no statistical significant difference ($p = 0.282$) comparing infectious complications from Europe versus Africa, Asia, and South America.

To assess factors for increased infectious complications after P-Bx, patients with infectious complications (n = 27) were compared with patients without infectious complications (n = 494) (Table 2). In multivariate analysis no significant association between UTI and any investigated variable was found (for all variables $p > 0.05$).

4. Discussion

Millions of men undergo P-Bx throughout the world each year as part of the accepted diagnostic pathway for prostate cancer [6]. Recently retrospective studies from Canada [7] and the United States [6] and one prospectively performed study from Europe [8] reported an apparent increase in the incidence of infective complications after transrectal P-Bx. In this study we found that just over 5% of men experienced symptomatic UTI after P-Bx, which resulted in serious morbidity in about 70% of cases with systemic symptoms and admission to hospitals. The rate of systemic infection found in our study is higher than earlier reports in the literature where a rate of 1% was quoted in one large study [11]. This finding is important because the low specificity of PSA testing means that cancer detection rates for initial P-Bx range between 22.8% and 42.0% [1]. A diagnostic procedure with a generally <50% positive detection rate should be as safe as possible.

Table 2 – Evaluation of possible risk factors comparing patients with versus without symptomatic urinary tract infections

Parameter	n	Symptomatic UTI (%)	No symptomatic UTI (%)	p value
Total	521	27/521 (5.2)	494/521 (94.8)	NA
Age, yr, median	521	66	67	0.411
Prostate size, ml, median	236	52	46	0.733
PSA, ng/ml, median	501	8	8	0.921
History of UTI	485	0/24 (0)	34/461 (7.4)	0.399
Preoperative bacteriuria*	130	0/9 (0)	5/121 (4.1)	1.000
Preoperative bowel preparation	521	12/27 (44.4)	186/494 (37.7)	0.543
History of antibiotic pretreatment	462	1/21 (4.8)	56/441 (12.7)	0.495
Antibiotic prophylaxis	518	27/27 (100)	484/491 (98.6)	1.000
Fluoroquinolone-based antibiotic prophylaxis	511	23/27 (85.2)	447/484 (92.4)	0.260
Antibiotic prophylaxis >1 d	511	18/27 (66.7)	327/484 (67.6)	1.000
Repeated P-Bx	516	8/25 (32.0)	100/491 (20.4)	0.204
Local anesthesia used	521	15/27 (55.6)	254/494 (51.4)	0.698
No. of biopsy cores, median	521	10	12	0.007
Histopathologic inflammation	448	5/21 (23.8)	140/427 (32.8)	0.479

UTI = urinary tract infection; NA = not applicable; PSA = prostate-specific antigen; P-Bx = prostate biopsy.

* In patients where urine culture was performed prior to prostate biopsy.

EAU guidelines classify transrectal P-Bx as a contaminated procedure and, if a urinary catheter or bacteriuria is present, as a dirty procedure [12] warranting antibiotic prophylaxis in all patients. Systematic review and meta-analysis of RCTs confirm that prophylaxis reduces the rate of bacteriuria following P-Bx, although the results for more clinically oriented outcomes such as symptomatic UTI are less certain [3]. These studies have so far focused on the use of fluoroquinolones and trimethoprim/sulfamethoxazole as suitable antibiotics for prophylaxis [3]. This is in line with pharmacokinetic studies in prostate tissue and prostatic secretions that confirm most orally administered fluoroquinolones achieve concentrations in the prostate that should be sufficient for the treatment of chronic bacterial prostatitis caused by susceptible pathogens [13]. High prostatic antibiotic concentrations are equally important in the prophylaxis of P-Bx. The superiority of fluoroquinolones was suggested by the results of a clinical pharmacokinetic study comparing ciprofloxacin (moderate prostatic tissue penetration) versus gentamicin (low prostatic tissue penetration) in prophylaxis against bacteremia following transrectal P-Bx. The study found that use of ciprofloxacin was associated with a lower incidence of bacteremia and clinical bloodstream infection, and this response correlated with higher prostate tissue levels of the drug [14]. There is as yet no consensus on the optimal duration of antibiotic prophylaxis for P-Bx. Our multinational study showed a median duration of 3 d, but there was no association between durations >1 d and the incidence of symptomatic UTI. EAU guidelines recommend single-dose prophylaxis for low-risk patients and prolonged courses of prophylaxis only in high-risk patients [5]; American Urological Association guidelines generally recommend prophylaxis for <24 h [4]. Because most men undergoing P-Bx are likely to have low levels of comorbidity, reducing the prophylaxis regimens to a single appropriately administered dose as recommended by the EAU guidelines would seem reasonable. This is important as part of the worldwide drive to reduce antibiotic selection pressure and thus decrease the emergence of antibiotic resistance.

Procedure-specific factors for a higher risk of infective complications after P-Bx are still not well defined, and our study was unable to add any further clarity on this issue [12]. It would seem appropriate to check a midstream urine culture prior to the procedure to rule out asymptomatic bacteriuria, which is recommended in the EAU guideline [5]. It is also recommended that in the presence of asymptomatic bacteriuria the prophylactic antibiotic regimen should include an agent tested susceptible to cover the urinary bacteria [5]. In our study, recommended preoperative patient evaluation by urine culture prior to biopsy [5] was performed in only 164 of 702 patients (23.4%) (Table 1). Adherence to guidelines could certainly be improved in this respect.

All other evaluated possible factors for increased infective complications were not significantly different between patients having symptomatic UTI and those who did not; however, diabetes as a risk factor was not investigated in this study. In a previous study it was found

that a larger prostate and diabetes were significantly associated with infective complications after P-Bx [8].

The observational epidemiologic design of our study collecting data at two time points in 2 yr prevented us from looking at changing patterns of infective complications and bacterial resistance over time. Further data collections at annual intervals over the coming years will allow us to achieve this goal. Our study also had insufficient power to be certain of identifying whether or not some of the risk factors examined were associated with the incidence of symptomatic UTI. The small sample size per participating site and in comparison with other studies therefore may have limited the conclusions from our study. Possible risk factors evaluating comorbidities such as diabetes, steroid use, or heart disease have not been evaluated, which is a limitation and will be taken up in subsequent study years. Our data on bacterial isolates do provide provisional support for the faecal carriage of fluoroquinolone-resistant bacteria as a risk factor for infective complications. A previous prospective study in consecutive patients undergoing P-Bx found that 22.0% of patients harboured ciprofloxacin-resistant *E coli* strains [15]. The study also found that faecal carriage of fluoroquinolone-resistant *E coli* strains was a significant risk factor for infective complications after P-Bx [15]. Specific fluoroquinolone-resistant *E coli* strains (eg, *E coli* ST131) could be detected as an important cause of sepsis after P-Bx [16]. It has also been shown that faecal fluoroquinolone-resistant *E coli* can even be selected by a single oral dose of 500 mg ciprofloxacin given for the prophylaxis of transrectal P-Bx [17]. The use of fluoroquinolones in the 6 mo before biopsy was also shown to be associated with an increased risk of faecal carriage of fluoroquinolone-resistant *E coli* strains [15]. Our study adds further credence to the emerging possibility that faecal carriage of fluoroquinolone-resistant *E coli* strains represents a significant risk factor classifying patients into a high-risk group for infective complications after P-Bx, particularly if, as seems likely, fluoroquinolones remain the most frequently used agents for prophylaxis. The rate of fluoroquinolone resistance amongst isolates from men with symptomatic UTI after P-Bx in the present study was particularly high (60%) compared with rates seen in other hospital settings that ranged from 22.7% to 30.8% [18]. Faecal fluoroquinolone-resistant bacteria as a risk factor could certainly explain the increase of infective complications after P-Bx, paralleling the worldwide increase of fluoroquinolone resistance in enterobacteria [10,19,20].

Strategies capable of decreasing infective complications after P-Bx must therefore be developed and evaluated so as not to dissuade healthy men who would benefit from early prostate cancer management from undergoing P-Bx when clinically indicated. Several strategies are currently debated, such as risk assessment to select patients at higher risk for infective complications, such as microbiological sampling of the faecal flora prior to biopsy to identify susceptibility to specific agents [21], change of biopsy route (eg, perineal P-Bx), and the evaluation of alternative antibiotics with improved susceptibility to be used for prophylaxis [22]. Antibiotic susceptibility is only one of the criteria for

recommending an alternative antibiotic. The pharmacokinetic distribution of the antibiotic within the prostate is equally important, as well as the suitability for this indication demonstrated in a clinical trial.

5. Conclusions

In this prospective multinational study on infective complications after P-Bx, a significant rate of infective complications after P-Bx was observed to be present worldwide. Our study supports the findings of others in suggesting that the presence of faecal fluoroquinolone-resistant bacteria is the most important risk factor. If this is the case, strategies to identify fluoroquinolone-resistant bacteria should be sought so as to decrease infective complications after P-Bx. This important and yearly performed ongoing study will deliver more data in the future and thus be able to address some of these important issues using a global perspective.

Author contributions: Florian M.E. Wagenlehner had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wagenlehner, van Oostrum, Çek, Naber, Bjerklund-Johansen.

Acquisition of data: Wagenlehner, van Oostrum, Çek, Grabe, Tandogdu, Tenke, Naber, Bjerklund-Johansen.

Analysis and interpretation of data: Wagenlehner, van Oostrum, Çek, Grabe, Tandogdu, Tenke, Pickard, Wullt, Pilatz, Weidner, Naber, Bjerklund-Johansen.

Drafting of the manuscript: Wagenlehner.

Critical revision of the manuscript for important intellectual content: Wagenlehner, van Oostrum, Çek, Grabe, Tandogdu, Tenke, Pickard, Wullt, Weidner, Naber, Bjerklund-Johansen.

Statistical analysis: Wagenlehner, van Oostrum, Pilatz.

Obtaining funding: Wagenlehner, van Oostrum, Çek, Grabe, Tenke, Naber, Bjerklund-Johansen.

Administrative, technical, or material support: van Oostrum.

Supervision: Wagenlehner, Naber, Bjerklund-Johansen.

Other (specify): None.

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Appendix. Participants in the 2010 and/or 2011 prostate biopsy Global Prevalence Study of Infections in Urology

Patients, n		Geographic region	Country	City	Center	Investigators
2010	2011					
1		Africa	Egypt	Alzahraa	Alzahraa University Hospital	Khaled Abdul Moneim
4		Africa	Egypt	Cairo	Ahmed Maher Teaching Hospital	Alaa Ahmed Hussein
	2	Asia	China	Changchun	The First Bethune Hospital, Jilin University	Yaowen Fu
12		Asia	Iran	Tehran	Hasheminejad Kidney Center	Reza Aghelmezhad
	2	Asia	Japan	Kitakyushu	University Hospital of Occupational and Environmental Health	Ryoichi Hamasuna
	1	Asia	Japan	Okayama	Okayama University Hospital	Koichiro Wada
18	11	Asia	Singapore	Singapore	National University Hospital	Fiona Mei Wen Wu
10	5	Asia	South Korea	Daejeon	Chungnam National University Hospital	Yong Gil Na
1		Asia	South Korea	Gwang-Ju	Chosun University Hospital	Seung Baik
2		Asia	South Korea	Seoul	St. Mary	Kim Sukju
5	1	Asia	South Korea	Suwon	St. Vincent Hospital	Seung-Ju Lee
2		Asia	South Korea	Uijeongbu	Uijeongbu St. Mary's Hospital	Chang Hee Han
	3	Asia	United Arab Emirates	Abu Dhabi	PMC	Medhat Ahmad Mohammad Elsayed
1		Europe	Bosnia-Herzegovina	Mostar	Regional Medical Center Mostar	Mustafa Bazardzanovic
	3	Europe	Bosnia-Herzegovina	Sarajevo	Clinical Center University of Sarajevo	Senad Bajramović
	5	Europe	Czech Republic	Liberec	Regional Hospital Liberec	Jan Mecl
3		Europe	Czech Republic	Nachod	County Hospital	Petr Prosvic
	9	Europe	Czech Republic	Opava	Slezska Nemocnice	Roman Stanek
21		Europe	Denmark	Aarhus	Aarhus University Hospital, Skejby	Pernille Skjold Kingo
16		Europe	Denmark	Fredericia	Fredericia Hospital, part of Hospital Littlebelt	Kim Hovgaard Andreassen
	18	Europe	Estonia	Tallinn	East-Tallinn Central Hospital	Aleksei Nelovkov
17		Europe	France	Suresnes	Hospital Foch	Cécile Bach and Henry Botto
	1	Europe	Germany	Brandenburg	Städtisches Klinikum Brandenburg GmbH	Jacqueline Wicht
1		Europe	Germany	Burgwedel	Großburgwedel (Klinikum Region Hannover)	Juliane Fiebich
7		Europe	Germany	Frankfurt	St. Katharinen Krankenhaus	Saskia Carmen Morgenstern
2		Europe	Germany	Gelsenkirchen	Bergmannsheil Buer	Stephan Miller
3	2	Europe	Germany	Giessen	Justus-Liebig-University	András Ruzs
	5	Europe	Germany	Marburg	Urological Office	Martin Ludwig

Appendix (Continued)

Patients, n		Geographic region	Country	City	Center	Investigators
2010	2011					
1		Europe	Germany	Sigmaringen	General Hospital Sigmaringen	Zoltan Varga
	1	Europe	Germany	Ulm	Bundeswehrkrankenhaus Ulm	Christian Löhmann
	1	Europe	Germany	Weiden	Klinikum Weiden	Bernhard Schwindl
	1	Europe	Greece	Aeghion	Aeghion General Hospital	Theodore Voudoukis
18	4	Europe	Hungary	Budapest	Jahn Ferenc South-Pest	Peter Tenke
15		Europe	Hungary	Budapest	Uzsoki Hospital	András Paczelt
18	22	Europe	Hungary	Pecz	University of Pecz	Szántó Árpád
	3	Europe	Hungary	Szeged	Albert Szent-Györgyi Clinical Center Faculty of Medicine	Ágnes Rosecker
	9	Europe	Hungary	Veszprém	Veszprém Megyei Csolnoky Ferenc Kórház Nonprofit Zrt	Sándor Gécs
	2	Europe	Italy	Andria	Bonomo Memorial Hospital	Angelo Guarriello
	13	Europe	Italy	Bolzano	General Hospital of Bolzano	Michele Lodde
10	16	Europe	Italy	Lecco	A. Manzoni	Alberto Trinchieri
2		Europe	Italy	Magenta	G. Fornaroli - Magenta	Sandro Danilo Sandri
4		Europe	Italy	Perugia	University of Perugia	Elisabetta Costantini
	3	Europe	Italy	Rome	Gemelli Hospital - Catholic University Medical School	Emilio Sacco
2	1	Europe	Italy	Trento	Santa Chiara Hospital	Tommaso Cai
4	1	Europe	Macedonia	Skopje	University Clinic of Surgery St. Naum Ohridski	Slobodan Petar Ristovski and Maja Sofronievska Glavinov
	23	Europe	Netherlands	Nieuwegein	St. Antonius Hospital	
1		Europe	Poland	Torun	Nicolaus Copernicus City Hospital	Przemyslaw Adamczyk
8	11	Europe	Portugal	Coimbra	Centro Hospitalar de Coimbra	Bruno Alexandre Guerra and Jorge Pereira
22		Europe	Portugal	Lisbon	Centro Hospitalar de Lisboa - Zona Central, Hospital de São José	Catarina Diogo Gameiro
4		Europe	Portugal	Matosinhos	Hospital Pedro Hispano	Tiago Pinto Correia
	1	Europe	Romania	Arad	Arad County Hospital	Dana Gabriela Negru
	5	Europe	Romania	Cluj Napoca	EndoPlus	Christian Nicolae Manea
	1	Europe	Russia	Moscow	Botkin Hospital	Lyubov Alexandrovna Sinyakova
1	6	Europe	Russia	Moscow	Moscow City Hospital 50	Andrey Vladimirovich Zaytsev
3		Europe	Russia	Togliatti	Municipal Health Care City Hospital #1	Rinat Khammatov
1		Europe	Russia	Moscow	S.R. Urology Institute	Perepanova Sergeevna Tamara
2	2	Europe	Russia	Ulyanovsk	Ulyanovsk State World War Veterans Hospital	Anton Maliavin
5		Europe	Slovakia	Kosice	L. Pasteur University Hospital	Jaroslav Beck
5		Europe	Slovakia	Poprad	Nemocnica Poprad a.s.	Lukas Kocis
	1	Europe	Spain	Langreo	Hospital Valle del Nalón	Miguel Alvarez Mugica
	10	Europe	Spain	Murcia	Virgen de la Arrixaca	Pedro López Cubillana
18	5	Europe	Spain	Pamplona	Hospital Virgen del Camino	Manuel Montesino-Semper
	5	Europe	Spain	Pamplona	Complejo Hospitalario de Navarra	Josep Campa
	12	Europe	Spain	Santa Cruz de Tenerife	Hospital Universitario de Canarias	David Hernández Hernández
	2	Europe	Spain	Tudela	Hospital Reina Sofia (Tudela)	Jose Angel Cuesta-Alcala
16		Europe	Sweden	Malmö	Malmö University Hospital	Magnus Grabe
4	1	Europe	Switzerland	Geneva	University Hospital of Geneva	Gregory Johann Wirth and Jacques Klein
7	12	Europe	Turkey	Edirne	Trakya University Hospital	Ersan Arda
14		Europe	Turkey	Erciyes	Erciyes University Department of Urology	Mustafa Sofikerim
	6	Europe	Turkey	Kocaeli	Kocaeli University Faculty of Medicine	
	1	Europe	Turkey	Kocaeli	Kocaeli Universitesi Hastanesi	Nazim Mutlu
1		Europe	Turkey	Konya	Selcuk University Meram Medical Faculty	Mehmet Kilinc
6	8	Europe	Turkey	Isparta	Suleyman Demirel University School of Medicine	Taylan Oksay
1		Europe	Turkey	Istanbul	Istanbul University Cerrahpasa School of Medicine	Sinharib Citgez
	4	Europe	Turkey	Istanbul	Istanbul Egitim Ve Araştırma Hastanesi	Soner Ulusoy
7		Europe	Turkey	Istanbul	Istanbul Hospital	Suleyman Erdinc Unluer
25	25	Europe	United Kingdom	Edinburgh	Western General Hospital	Roland Donat
6		Europe	United Kingdom	Salford	Salford Royal Foundation Trust	Laura Derbyshire
3	20	Europe	United Kingdom	Stoke on Trent	University Hospital of North Staffordshire	Mark Fraser Saxby
	1	Europe	Ukraine	Donetsk	University Clinic	Kolesnikov Vladimir Stanislavovich

Appendix (Continued)

Patients, n		Geographic region	Country	City	Center	Investigators
2010	2011					
17		South America	Argentina	Buenos Aires	Hospital Italiano	Maria Ines Staneloni
6		South America	Argentina	Buenos Aires	Instituto Quirurgico del Callao-Sanatorio Anchorena	Javier David Altclas
2		South America	Argentina	Salta	El Carmen	Jose Ignacio Militello
	10	South America	Brazil	Florianópolis	Centro de pesquisas oncologicas de Santa Catarina	Flavio Heldwein

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