

The Effect of Evolving Strategies in the Surgical Management of Organ-Confined Prostate Cancer: Comparison of Data from 2005 to 2014 in a Multicenter Setting

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ABSTRACT

Introduction: The objective of this study was to evaluate changes of patient characteristics and surgical techniques in radical prostatectomy in Germany within the last decade.

Methods: Data from 44 German prostate cancer centers were included in the study. Patients' characteristics (age, initial PSA value), surgical techniques (open vs. minimally invasive approaches), perioperative parameters

(operating time, rate of nerve-sparing (NS) radical prostatectomies (RPs), hospitalization time, catheter indwelling time, surgical margin status, number of dissected lymph nodes (LN)), and pathological findings (tumor stage, Gleason score) were analyzed.

Results: Data from 11,675 patients who underwent RP between 2005 and 2014 were analyzed. The rate of open RP approaches decreased by 1.7% ($p = 0.0164$), the rate of minimally invasive approaches increased by 1.8% ($p = 0.0164$). Robot-assisted RPs (RARP) increased by 4.6% ($p < 0.0001$). The number of NS procedures and pelvic lymphadenectomy (LA) increased by 4.5% ($p < 0.0001$) and 4.7% ($p < 0.0001$), respectively. Catheter indwelling time and hospitalization time decreased by 1 day ($p < 0.0001$). No change in the rate of positive surgical margins ($p = 0.5061$) and the ratio of positive lymph nodes removed ($p = 0.4628$) was observed. The number of Gleason ≤ 6 tumors decreased significantly ($p < 0.0001$).

Conclusions: The number of RARP has significantly increased over the past decade and there is a trend towards surgeries on more advanced tumors with higher yields of lymph nodes dissected. At the same time, the rate of

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nerve-sparing procedures has significantly increased.

Keywords: Gleason; Prostate cancer; Radical prostatectomy; Robot-assisted RP; Surgical techniques

INTRODUCTION

Prostate cancer is one of the most common malignancies in men with more than 1 million new cases being diagnosed worldwide every year [1]. Despite a 5-year relative survival rate of 99.7% for all pathological stages, prostate cancer remains the second leading cause of cancer deaths in men [2, 3].

With the introduction of prostate-specific antigen (PSA)-based prostate cancer screening in the early 1990s, the annual number of radical prostatectomies (RPs) performed in Germany constantly increased until 2007 (source: Federal Statistical Office in Germany). The relatively new concept of active surveillance (AS) for low-risk prostate cancer and the introduction of several alternative treatment options in addition to modern radiation therapy have led to a decrease of RP numbers performed in Germany from 28,374 in 2006 to 21,850 in 2013 [4]. This translates into a decline of approximately 930 RPs per year throughout all prostate cancer centers in Germany and does not necessarily reflect a “paradigm shift” towards active surveillance as stated in the literature earlier [5].

Today, a patient’s individual decision between surgery or alternative approaches is not just based on relatively objective clinical parameters; instead, individual factors such as family considerations, social environment, social status, and factors like comorbidities, patient–consultant relationship, and logistic factors, such as accessibility to

hospitals and to the latest surgical techniques, are gaining more and more importance [6].

While the number of RP procedures has decreased over the last decade, the technological progress made in the performance of RP procedures has increased especially since the introduction of the robot-assisted radical prostatectomy (RARP) in 2000 [4, 7]. In the USA, RARP already represents the most frequently used surgical approach for treatment of localized prostate cancer. Current data suggests that in 2008, 80% of RPs in the USA were already robot-assisted and the numbers are increasing [8, 9]. In comparison, the proportion of robot-assisted prostatectomies in Germany was 25.2% in 2013 [4].

Data from the literature and from the Federal Statistical Office in Germany suggest a trend towards an increase of minimally invasive RP procedures performed in Germany over recent years; however, no distinction was made between conventional and robot-assisted laparoscopy [10]. The purpose of this study was to analyze the time trends with respect to the utilization of RARP and conventional open RP procedures performed in 44 German prostate cancer centers over the last 9 years.

METHODS

A retrospective analysis of prostate cancer patients who underwent RP between 2005 and 2014 was performed using an Internet-based German database (<http://www.prostata-ca.net>) that has been coordinated by the Berlin Cancer Center (Berliner Tumorzentrum) since 2005. The following parameters were evaluated in the analysis: age, PSA value, RP technique, duration of the surgery, nerve-sparing technique, hospitalization time, catheter indwelling time, surgical margin status, performance of lymph node

dissection, lymph node involvement, pathologic Gleason scores, and pathologic tumor stage. The data was filtered (Excel 2013) according to internal plausibility criteria and subdivided into two groups: patients who underwent RP between 2005 and 2009 and patients who underwent RP between 2010 and 2014.

We compared the clinical and pathological characteristics of the study cohorts using Chi-square test and Fisher exact test for categorical variables and the Mann–Whitney test for continuous variables. A p value less than 0.05 was considered statistically significant. All statistical analyses were performed using GraphPad Prism Version 5.00.

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethics Guidelines

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

RESULTS

Data from over 34,772 prostate cancer patients who underwent RP in one of the participating 44 German centers between 1985 and 2014 were analyzed. Patients with missing data, such as date of surgery and date of discharge from the hospital, were excluded from the study. This resulted in 11,675 datasets from 2005 to 2014 available for analysis.

The data from patients who underwent RP between 2005 and 2014 was subdivided into two

eras: the era between 2005 and 2009, which included data from 6600 patients, and the era between 2010 and 2014, which included data from 5075 patients.

The mean age at the time of surgery of men operated on between 2005 and 2009 was 65.0 years, while the mean age of patients operated on in the second era was 65.7 years (median 66.0 vs. 66.7, $p < 0.0001$). There was no statistically significant difference in the mean initial PSA values between both eras.

The ratio of open RPs has decreased significantly by 1.7% (81.9% vs. 80.2%, $p = 0.0164$) in the analyzed time period mainly because of a decrease in perineal RPs by 1.2% (7.9% vs. 6.7%, $p = 0.0153$). Minimally invasive procedures increased by 1.8% (18.0% vs. 19.8%, $p = 0.0164$) because of an increase of RARPs by 4.6% (0.02% vs. 4.6%, $p < 0.0001$). The classic transperitoneal laparoscopic approach (LRPE) decreased significantly (12.9% vs. 10.3%, $p < 0.0001$). No difference was found in the percentage of endoscopic extraperitoneal approaches (EERPE) ($p = 0.6484$) (Table 1, Fig. 1).

The median operation time of RP procedures was 9 mins longer in the era between 2010 and 2014 than it was between 2005 and 2009 (144 vs. 153 min, $p < 0.0001$). In 2010–2014 the rate of nerve-sparing techniques was significantly more utilized compared to 2005–2009 (58.7 vs. 63.2%; $p < 0.0001$). The median hospitalization time decreased by 1 day (9 vs. 8 days, $p < 0.0001$), as did the catheter indwelling time (9.9 vs. 8.9 days, $p < 0.0001$). There was no difference observed between the two eras concerning the surgical margin status ($p = 0.5061$). The mean number of dissected lymph nodes increased from 6.9 to 8.9 ($p < 0.0001$), while the percentage of positive nodes remained unchanged (4.0 vs. 3.1, $p = 0.4628$). Furthermore, there was a significant increase in the rate of pelvic lymphadenectomies

Table 1 Overview over the changes in surgical techniques over time

RP technique	Era 2005–2009	Era 2010–2014	Difference	<i>p</i> value
Percentage perineal RP (%)	7.9	6.7	−1.2	0.0153
Percentage retropubic RP (%)	74.0	73.5	−0.5	0.5037
Percentage of all open RP (%)	81.9	80.2	−1.7	0.0164
Percentage of robot-assisted RP (RARP) (%)	0.02	4.6	4.6	0.0001
Percentage of endoscopic extraperitoneal RP (EERPE) (%)	5.1	4.9	−0.2	0.6484
Percentage of laparoscopic transperitoneal RP (LRPE) (%)	12.9	10.3	−2.6	0.0001
Percentage of all minimally invasive RP (%)	18.0	19.8	1.8	0.0164

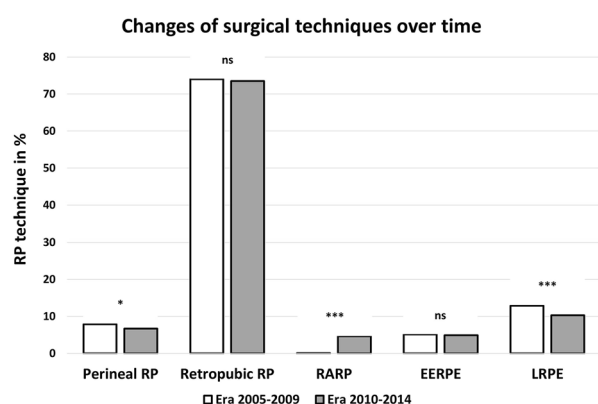


Fig. 1 Changes in the surgical management of prostate cancer: comparison of data from 2005–2009 vs. 2010–2014

performed between 2005 and 2014 (69.7% vs. 74.4%, *p* < 0.0001) (Table 2).

Between 2010 and 2014 there were fewer tumors operated on with pathologic Gleason scores ≤6 than between 2005 and 2009 (4.1% vs. 1.0% and 25.3% vs. 19.5%, *p* < 0.0001). The percentage of Gleason 7a (3 + 4) tumors remained constant and there was a significant increase of Gleason 7b (4 + 3) (16.3% vs. 19.7%, *p* < 0.0001), Gleason 9 (6.1% vs. 10.2%, *p* < 0.0001), and Gleason 10 (0.2% vs. 0.6%, *p* = 0.0020) tumors (Table 3; Fig. 2).

While there was no change in the percentage of pT2a and pT3a tumors being operated on between 2010 and 2014 compared to between

2005 and 2009, there were significantly less pT2b (2.8% vs. 1.6%, *p* < 0.0001) and less pT2c tumors (54.5% vs. 52.3%, *p* = 0.0321). In contrast, the percentage of tumors with seminal vesicle invasion (pT3b) increased significantly (12.8% vs. 15.8%, *p* < 0.0001). The percentage of tumors that invade the bladder and rectum (pT4) decreased between 2010 and 2014 compared to between 2005 and 2009 (1.9% vs. 0.9%, *p* < 0.0001) (Table 4, Fig. 3).

DISCUSSION

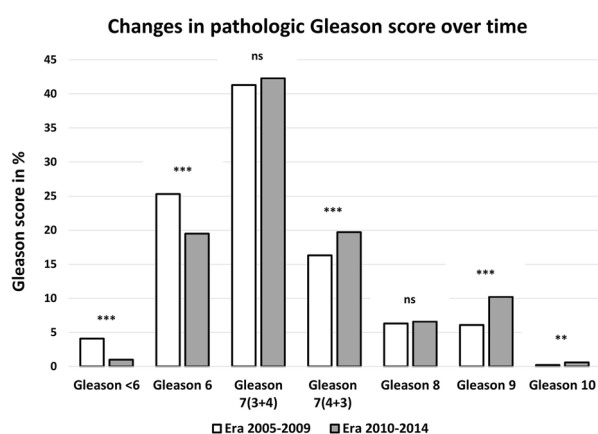
Over recent years there has been a significant change in the management of localized prostate cancer. As a result of recommendations against PSA testing and screening there has been a decline in RPs as well as pelvic lymph node dissection (PLND) and high dose rate (HDR) brachytherapy over recent years [11, 12]. Furthermore, more and more patients with low-risk tumors are included in active surveillance programs; patients with locally advanced disease or lymph node metastases are treated in multimodal concepts with surgery and consecutive radiation therapy. At the same time, the implementation of robot-assisted surgery has led to a broader availability of minimally invasive procedures for the

Table 2 Comparison of perioperative parameters over time

Perioperative parameter	Era 2005–2009	Era 2010–2014	Difference	<i>p</i> value
Median operating time (min)	144.0	153.0	9.0	0.0001
Rate of nerve-sparing operations (%)	58.7	63.2	4.5	0.0001
Median hospitalization time (days)	9.0	8.0	−1.0	0.0001
Median catheter indwelling time (days)	9.9	8.9	−1.0	0.0001
Positive surgical margin R1 (%)	25.8	25.6	−0.2	0.5061
Mean number of dissected lymph nodes	6.9	8.9	2.0	0.0001
% positive lymph nodes	4.0	3.1	−0.9	0.4628
Rate of pelvic LA (%)	69.7	74.4	4.7	0.0001

Table 3 Pathologic outcomes: proportion of patients with different pathologic Gleason scores

Pathologic Gleason score	Era 2005–2009	Era 2010–2014	Difference	<i>p</i> value
Gleason <6 (%)	4.1	1.0	−3.1	0.0001
Gleason 6 (%)	25.3	19.5	−5.8	0.0001
Gleason 7(3 + 4) (%)	41.3	42.3	1.0	0.2875
Gleason 7(4 + 3) (%)	16.3	19.7	3.4	0.0001
Gleason 8 (%)	6.3	6.6	0.3	0.523
Gleason 9 (%)	6.1	10.2	4.1	0.0001
Gleason 10 (%)	0.2	0.6	0.4	0.002

**Fig. 2** Changes in the pathologic Gleason scores over time treatment of prostate cancer. These trends were also apparent in our database.

The current analysis has shown significant changes in the surgical management of prostate

cancer: our data showed fewer surgeries of patients with low-risk tumors, while more patients with intermediate- and high-risk cancer were operated on.

Our study showed an increase in the mean age of men undergoing RP from 65.0 to 65.7 years. This seems to be consistent with other findings in the literature that suggest an overall trend to operate on older patients today than was the case 10–15 years ago: single-center data from a European tertiary-care institution (Martini-Klinik) showed a mean patient age increase of 3 years in men who underwent RP over a time frame of 9 years between 2000 and 2009 [13]. Furthermore, an analysis from the Federal Statistical Office in Germany that evaluated all RPs performed in Germany in the

Table 4 Pathologic outcomes: pathologic tumor stages

Pathologic T stage	Era 2005–2009	Era 2010–2014	Difference	<i>p</i> value
pT2a (%)	10.7	10.3	−0.4	0.6226
pT2b (%)	2.8	1.6	−1.2	0.0001
pT2c (%)	54.5	52.3	−2.2	0.0321
pT3a (%)	17.1	18.5	1.4	0.0545
pT3b (%)	12.8	15.8	3.0	0.0001
pT4 (%)	1.9	0.9	−1.0	0.0001

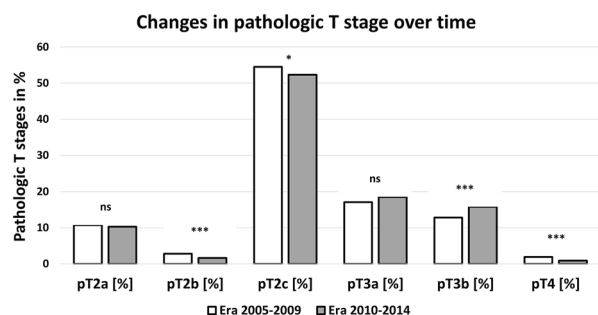


Fig. 3 Changes in the pathological T stage

years 2013 and 2014 showed that in 2014, fewer younger men (age 45–75) and more older men (age 75–85 and age 90–95) underwent RP compared to in 2013. Interestingly, this data also showed that in 2014 fewer men were operated on in the age group of 85–90 years than was the case in 2013 (source: Federal Statistical Office in Germany).

While no difference in the mean initial PSA value over time was apparent in our analysis, data from the Martini-Klinik showed a decrease from 10.2 to 9.1 ng/ml in the mean PSA between the years 2000 and 2009 [13]. As our analysis, however, included data from 44 prostate cancer centers in Germany, this finding might reflect clinical reality better than data from a single center.

The current study shows that the introduction of RARP implemented in more and more centers led to a decrease of open RPs

during the study period of 9 years. Data from the literature shows that while 1.5% of all hospitals in Germany performed RPs using a robot in 2006, this rate increased to 13% in 2013 [4]. The increase of RARP in our data was 4.6% over the study period and does not necessarily reflect the reality in German treatment; this discrepancy could be explained by the fact that most of the participating prostate cancer centers did not offer robot-assisted surgery. However, the increase of RARP procedures by 4.6% in 44 German centers within 9 years seems to draw a realistic picture when comparing our data with data from the Federal Statistical Office which evaluated the overall number of laparoscopic procedures from all prostate cancer centers in Germany: the rate of all laparoscopic RPs has increased by 23.2% (13.4% in 2007 vs. 36.6% in 2014) within 7 years and open RP approaches decreased by 23.1% (85.8% in 2007 vs. 62.7% in 2014, *p* < 0.0001).

Therefore, by not exclusively analyzing data from high volume centers like in the current study the clinical reality in Germany might be reflected quite realistically. However, one has to keep in mind that the number of RARPs is increasing rapidly, especially over the past 2 years, and that even recent data might be outdated quickly. Overall, although the frequency of RARP has increased significantly

over the last few years, Germany is still at another level compared to the USA, where currently 70–85% of all RPs are performed with a robot-assisted approach [8, 9].

The analysis of perioperative parameters in this study showed an increase in the operation time by 9 mins (144 vs. 153 min, $p < 0.0001$), an increase in nerve-sparing procedures by 4.5% ($p < 0.0001$), a shorter hospitalization time (9 vs. 8 days, $p = 0.0001$), and a shorter catheter-indwelling time (9.9 vs. 8.9 days, $p = 0.0001$), over the last 9 years. The increase in the operating time could most likely be explained by the increase in the usage of robot-assisted surgery: according to data in the literature, the operation time with RARP is significantly longer compared to the operation time with open surgery (184.4 vs. 128 min) [14]. Furthermore, the more frequent performance of nerve-sparing procedures might have contributed to a longer surgical time.

Our data showed an increase in nerve-sparing procedures by 4.5% over study period of 9 years (58.7% vs. 63.2%, $p < 0.0001$). This confirms the desire to achieve better functional outcomes after surgery which can be explained by the demographic changes in highly developed countries and better education of patients concerning the preservation of continence and erectile function. Unfortunately, we were not able to extract postoperative functional data from the database. Therefore we cannot conclude that the higher rate of nerve sparing resulted in a lower rate of erectile dysfunction following RP [7, 15].

In patients included in our analysis the median hospitalization time as well as the catheter-indwelling time both significantly decreased by 1 day during the study period of 9 years (9 vs. 8 days, 9.9 vs. 8.9 days, $p < 0.0001$). Beside the general aspects of

changing healthcare systems and the related economic reasons in hospitals to keep hospital stays for patients as short as possible, these findings can also be explained by the fact that according to data in the literature RARPs not only promise better functional but also better perioperative outcomes, e.g., a shorter hospitalization and catheter indwelling time with RARP compared to open RP [7, 14, 16]. A similar analysis of data from the same database showed that hospitalization time decreased by 2 days between 2005 and 2008 (10 vs. 8 days) [10]. One argument of the advocates of RARP is the reduced length of hospitalization and therefore improved quality of life for the patient [8]. However, there are also other studies that show similar perioperative, oncological, and functional outcomes for laparoscopic RP compared to open and robotic RP if surgeons were high volume surgeons [17].

In our analysis of patients operated on between 2005 and 2014 we showed a significant increase in the number of lymph node dissections performed during RP (69.7% vs. 74.4%, $p < 0.0001$). We also demonstrated that there has been a trend to operate on more intermediate- and high-risk tumors (Gleason 7b, 8, 9, and 10) in the more recent era compared to 9 years ago (Table 3). These findings of an increase in lymph node dissections and an increase in the surgery of high-risk prostate cancers are closely connected and can be explained by recently published findings which showed that a multimodal approach with RP combined with an extended lymphadenectomy and/or adjuvant radiotherapy can improve mortality up to 10–15%, especially in high-risk patients [18]. Additionally, the increase in lymph node dissection is one of the main characteristics that may be related to the use of RARP. It has been described recently that pelvic lymph node

dissection was more frequently performed at RARPs (71.6%) compared to open RPs (66.2%) [19].

The analysis of histopathological data documented in our database showed a trend towards the surgery of fewer low-risk tumors (Gleason ≤ 6) and more intermediate- and high-risk tumors over the last 9 years in Germany: the rate of Gleason < 6 tumors operated on decreased by 3.1% (4.1% vs. 1.0%, $p < 0.0001$) and the rate of Gleason 6 tumors by 5.8% (25.3% vs. 19.5%, $p < 0.0001$) while the rate of Gleason 7b (16.3% vs. 19.7%, $p < 0.0001$), Gleason 9 (6.1 vs. 10.2%, $p < 0.0001$), and Gleason 10 (0.2% vs. 0.6%, $p = 0.0020$) tumors operated on increased significantly. The rate of Gleason 7a and Gleason 8 tumors operated on remained constant. Although when looking at the overall numbers of RPs performed in Germany active surveillance still seems under-represented, the decrease of the ratio of Gleason ≤ 6 tumors being operated on according to our data suggests that there is at least a trend towards higher active surveillance rates in low-risk patients. This is also reflected in the analysis of the pathologic tumor stage: while we observed an increase in advanced pT3b tumors (12.8% vs. 15.8%, $p < 0.0001$) we could demonstrate a decrease in pT2b and pT2c tumors (2.8% vs. 1.6%, $p < 0.0001$, 54.5% vs. 52.3%, $p = 0.0321$). This is in line with recently published data from the USA that also demonstrated a significant increase of T3a and T3b tumors undergoing RP between 1998 and 2012 while alternative therapies like radiation therapy decreased [20].

Further evaluation of the data from this database is needed to analyze the ratio of patients that have undergone active surveillance. Current literature from other countries showed that 15% of all patients

diagnosed with prostate cancer are already on active surveillance [21]. Our analysis did not include data about the number of positive biopsies, the ratio of cancer within this biopsy, or any information about the clinical T stage of these patients, which is essential for clinical decision-making. Additionally, before drawing conclusions from the data analyzed in this study one has to take into account the weaknesses of data arising from a multicenter Internet-based database like this. As there are typically no study nurses or dedicated clinical staff in the different centers responsible for ensuring a timely and correct documentation of complete data in all patients, the integrity of the different parameters is not always given. Thus, one major limitation of the current study is the high percentage of patients with missing data and/or lost to follow-up, which could have resulted in a selection bias. Nevertheless, this database is one of the biggest sources of data on RP in Germany and therefore it most likely represents the clinical reality in Germany.

CONCLUSION

Our data confirms the trend towards modern laparoscopic surgical techniques. In particular, robot-assisted radical prostatectomy is gaining more and more importance across a broad range of prostate cancer centers in Germany. Furthermore, we demonstrated a decrease in low-risk prostate cancer patients who underwent RP. At the same time more intermediate- and high-risk prostate cancer patients are currently treated surgically. Functional outcomes like the preservation of erectile function and continence are gaining more and more importance due to the raising awareness and better education of patients as well as the use of robotic systems.

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Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Data Availability. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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