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Original scientific paper

Evolution of the Clinical Presentation and Outcomes after Radical Prostatectomy for Patients with Clinically Localized Prostate Cancer – Changing Trends over a Ten Year Period

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A B S T R A C T

We demonstrate the evolution of the clinical presentation and outcomes for patients with clinically localized prostate cancer (PC) treated with radical retropubic prostatectomy (RRP) at our department, emphasizing epidemiologic significance of changes during the 10-year period. We assessed the annual trends for changes in patients age, preoperative prostate specific antigen (PSA), preoperative versus postoperative stages and Gleason grades, organ confined status and surgical margin status. A total of 488 RRPs were performed from January 1996 to December 2005 with the annual frequency increased from 8 to 129 (1512.5%). Mean patient age increased from 61.5 to 66.12 years in 2005, with the percentage of men aged more than 70 years increased from 12.5 to 26.5%, respectively. The detection of PC based solely on pathological PSA levels (as indication for prostate biopsy) rose impressively from 25.5 to 70% and the rates of postoperative organ-confined disease also increased significantly from 25 to 74.7%. Mean preoperative PSA decreased from 16.7 to 9.89 ng/mL. On the contrary, there was an increase in percentage of patients with preoperative PSA values ranging from 4 to 10 ng/mL (from 20 to 65.4%). Positive surgical margin rate decreased from 49.4 to 25% and percent of patients receiving neoadjuvant therapy decreased from 78.5 to 5.4%. Proportion of patients who were undergraded decreased from 75.1 to 31.7%. The rates of understaging have remained relatively stable over the years. During the study period, PC was increasingly detected by prostate biopsy on the basis of a pathological PSA level only and shifted significantly to more organ-confined stages with more favourable outcomes for pathological variables due to a more accurate assessment of clinical stage prior to surgery, reduced use of neoadjuvant therapy and improved surgical technique. Our data also argue strongly that routine PSA testing should be expanded and not restricted.

Key words*: prostate cancer, localized prostate cancer, prostate specific antigen, digital rectal examination, radical retropubic prostatectomy, outcome*

Introduction

The incidence of prostate cancer (PC) has increased worldwide during the past fifteen years[1,2]. This trend may be a result of the widespread application of prostate specific antigen (PSA) testing and increased life expectancy[2]. It is the most common non-skin cancer in men in the United States, and is second only to lung cancer as a cause of cancer deaths in men[3]. In Croatia, it is the second most common cancer in men (second only to lung cancer)[4,5]. Prior to the widespread use of PSA testing in asymptomatic men, PC was detected mainly via digital rectal exam (DRE), increased prostatic phosphatase levels and after transurethral resection; and only 25% of newly diagnosed PCs were clinically organ-confined after surgery[6,7]. Since the advent of PSA testing in Western countries, the percentage of newly diagnosed organ-confined and locally advanced disease has increased to upwards of 80%[3]. With no PSA screening programme, such a dramatic change has not been reported in Croatia, but

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there has been a significant increase in the annual detection rate since the introduction of PSA testing in early 90s. The operative management of localised PC has undergone important changes in the past decade, with major improvements in surgical technique, a greater emphasis on structured preoperative staging and assessment of quality of life. Radical retropubic prostatectomy (RRP) and recently, laparoscopic radical prostatectomy, has become the preferred treatment for selected patients with early stage PC and today, it remains the gold standard for treatment of localised PCs with favourable prognoses (i.e., tumor stage T1a-T2, PSA<10 ng/mL, and biopsy Gleason score<7)[8,9]. The 10-year cancer-specific survival rate of RRP was recently reported to be 90%[10]. The treatment is highly effective; therefore, patients usually enjoy long-term survival, indicating that the treatment should guarantee a high quality of life. With an increasing chance of finding early stage PC, the procedure has also gained popularity among Croatian urologists in several hospitals over the last decade.

Purpose of this epidemiologic report is to evaluate our experience in RRP. We retrospectively evaluated the preoperative and postoperative data of patients who underwent RRP for localized PC in our institution. Changes and advances in patient selection criteria over time and clinical outcome data are evaluated and discussed emphasizing annual changes over ten year period.

Material and Methods

We retrospectively analyzed preoperative clinical data and outcomes of 488 consecutive patients treated with RRP for clinically localized PC at our institution (Department of Urology »Sestre milosrdnice« University hospital, Zagreb, Croatia) between January 1996 and December 2005.

A computerized database was created and data abstracted directly from the records; the information abstracted and entered included the date of surgery, the age of the patient, the medical history regarding use of neoadjuvant therapy (antiandrogens for 3 months prior to RRP), preoperative serum PSA level, clinical stage (DRE status), prostate biopsy Gleason grade and number of biopsy cores sampled, the final pathological stage and grade and surgical margin status. The last PSA value and DRE status obtained prior to prostate biopsies was used in the analysis. Patients underwent a bilateral staging pelvic lymphadenectomy with or without frozen section, followed by a RRP under general anaesthesia. The RRP was carried out using the similar technique as originally described by Walsh, with small modifications, depending on the surgeon[11]. All procedures were performed by urologists at our department with different surgical skills and experience. The frozen section analysis after pelvic lymphadenectomy was carried out only in patients with higher risk for extraprostatic extension of the disease (PSA>20 ng/mL, and biopsy Gleason score>7). The RRP specimens, including prostate, seminal vesicles, and bilateral pelvic lymph nodes, were examined microscopically after routine preparation. All specimens were scored according to the Gleason grading system[12]. Microscopic extension of malignant cells to the inked surface of the resected specimen was interpreted as a positive surgical margin. The patients were staged according to the 2002 TNM staging criteria[13].

Preoperative and postoperative clinical and pathological data were analyzed and compared for annual changes over the observation period. Descriptive statistics and time-flow charts were used to analyze trends over time (calendar year).

Results

A total of 488 men underwent RRP for localized PC at our department between January 1996 and December 2005, with the annual frequency of surgical interventions increased markedly, from 8 to 129 (1512.5%) during the observation period. In 24 cases with gross lymph node metastasis at frozen section, only bilateral lymph node dissection was done and the proportion decreased rapidly over the study period due to more accurate preoperative staging and more rigorous selection of patients suitable for surgery (lower PSA levels, lower biopsy Gleason grades). Overall, there was no early peri-operative mortality. Figure 1 demonstrates an increase in RRP rate, especially in last two years with more than two hundred operations performed.

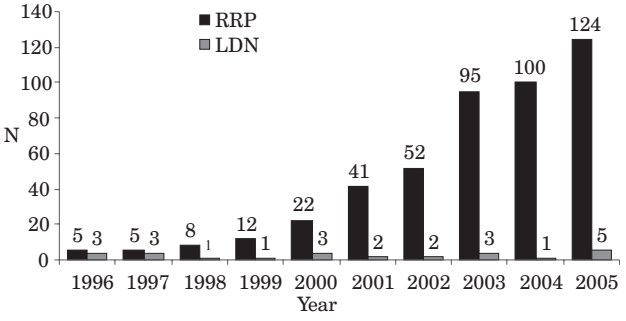

Fig. 1. The number of patients undergoing RRP in 1 year intervals, RRP – radical retropubic prostatectomy, LDN – lymphadenectomy only due to ex- tempore positive lymph nodes.

The distribution of preoperative (clinical) tumour stage with time is illustrated in Figure 2. It shows the dramatic stage migration occurring in the PSA era. The contribution of preoperative cT1c disease, based solely on pathological PSA levels as indication for prostate biopsy (DRE negative), rose significantly, from 25.5% in 1996 to 75% in 2005.

Mean age of patients at diagnosis was 61.5 years in 1996. It is gradually increasing yearly and in 2005 it was 66.12 years (overall range 44 to 75 years) (Figure 3). The annual rates of those aged greater than 70 years old were 12.5%, 7.7%, 16%, 20.4%, 19.4%, 22.6%, 25.8%, 25.6%, 24.7% and 26.1%, respectively.

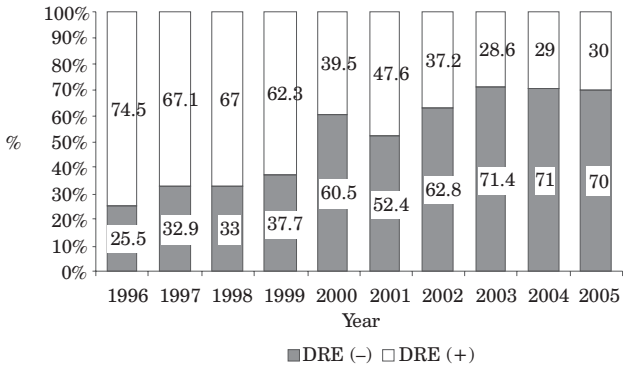

Fig. 2. Preoperative stage migration: the contribution of nonpalpable disease (cT1c, DRE(-)), detected solely on pathological PSA levels.

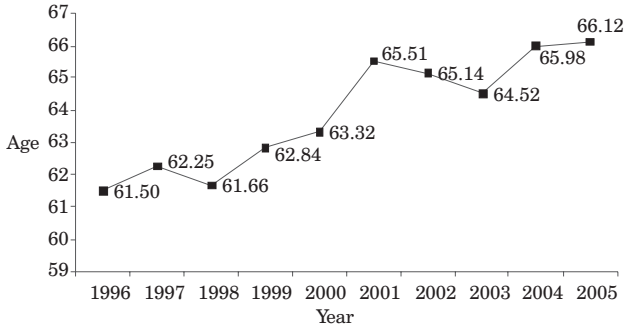

Fig. 3. Mean age of patients treated operatively for localized PC.

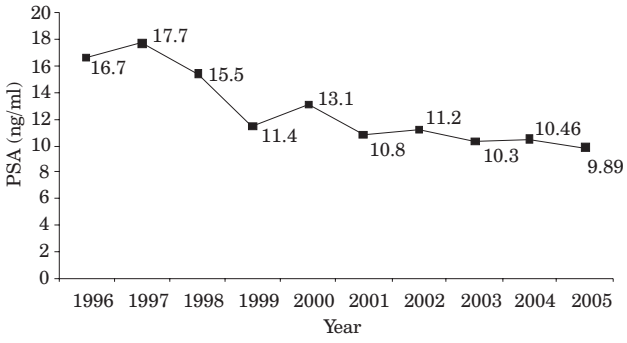

Fig. 4. The annual changes in mean preoperative serum PSA value.

Mean preoperative PSA value has gradually decreased from 17.7 ng/mL in 1996 to 9.89 ng/mL in 2005 (overall range 0.4 to 51 ng/mL) (Figure 4). On the contrary, distribution of preoperative PSA values over time demonstrates increase in percentage of patients with preoperative PSA values ranging from 4.0 to 10.0 ng/mL (from 20% in 1996 to 65.4% in 2005) (Figure 5).

Traditionally, for patients with abnormal PSA values and/or abnormal DRE findings, six core transrectal ultrasound (TRUS) guided prostate biopsies were performed (from 1994 to 1997). The rates of patients with eight and more cores per biopsy taken increased markedly and were 0%, 0%, 10%, 23%, 28%, 27%, 31%, 40%, 49% and 80% in the observation period indicating a tendency for more accurate sampling of the prostate tissue and more accurate preoperative staging of prostate cancer.

Of 488 patients, 150 (30.7%) received neoadjuvant therapy for more than 3 months prior to RRP. The annual rates of patients receiving neoadjuvant therapy markedly decreased and were 78.5%, 75.2%, 44.3%, 46%, 34.9%, 36.1%, 33.1%, 23%, 15.3% and 5.4% the observation period, respectively (Figure 6).

The distribution of postoperative tumour stages with time is shown in Figure 7. Annual distributions of postoperative pT2 and pT3 stages demonstrate migration toward localized disease. Annual rates of postoperative pT2 (organ confined disease) stages were 25 %, 37.5%, 44.4%, 46.3%, 72.7%, 76.2%, 62.7%, 71.4%, 73% and 74.7%, from 1996 to 2005 (Figure 7).

The proportion of patients with margin positivity decreased steadily during the observation period, from 49.4% in 1996 to 25% in 2005, which also reflects advancements in surgical skill and more rigorous patient selection criteria over the observation period (Figure 8).

Diagram showing changes in distribution of preoperative Gleason grades indicates tendency of the pathologist to assign a higher Gleason grade in prostate biopsy specimens (Figure 9), so there is significant decline in undergrading over the years (from 75.1% in 1997 to 31.7% in 2005) (Figure 10).

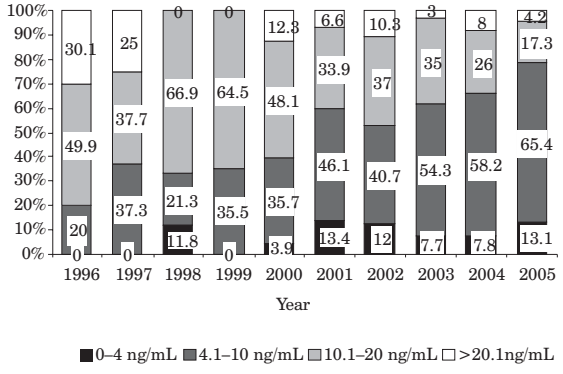

Fig. 5. Change in distribution of preoperative serum PSA values over time.

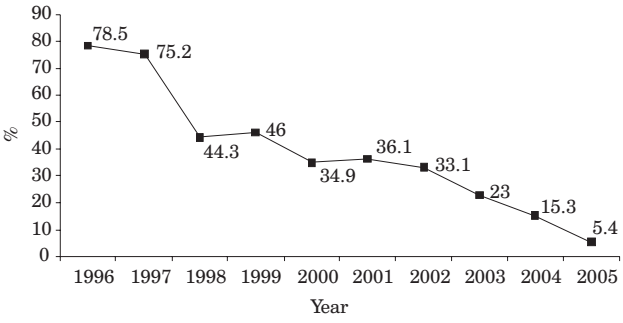

Fig. 6. The annual rates of patients receiving neoadjuvant therapy prior to RRP.

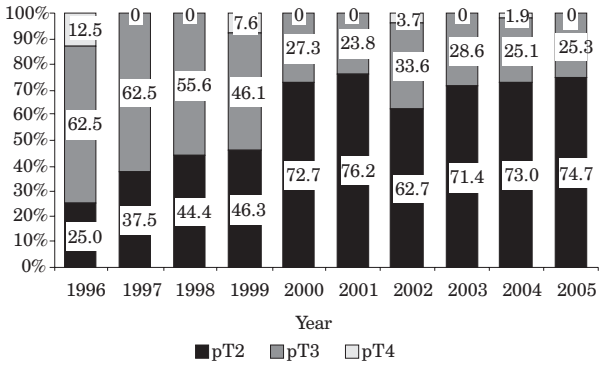

Fig. 7. Postoperative stage migration: the contribution of organ confined disease (pT2).

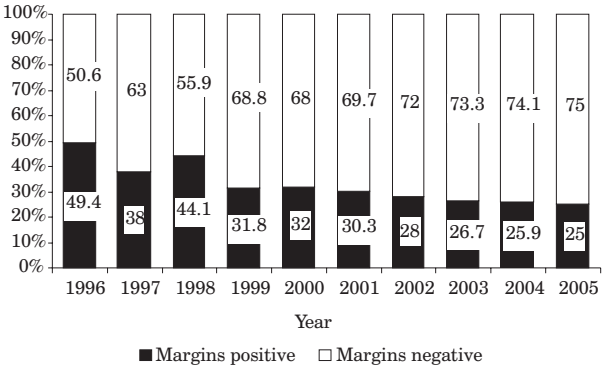

Fig. 8. Surgical margin status after RRP over the study period.

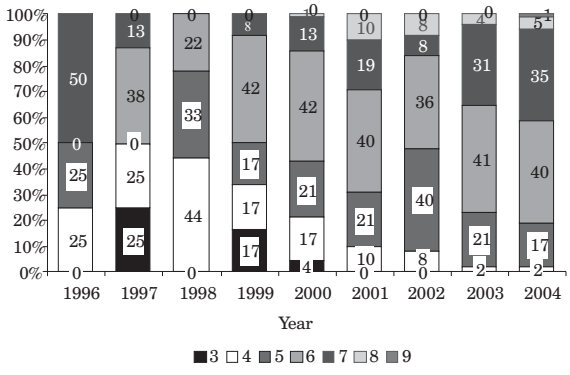

Fig. 9. Changes in distribution of preoperative (biopsy) Gleason grades.

The rates of patients who were understaged were 60.0%, 50.0%, 66.7%, 76.9%, 64.0%, 51.2%, 72.2%, 64.3%, 67.3% and 77%, over the years (Figure 11).

Discussion

Serum PSA testing is now a commonly used method for detecting organ-confined PC amenable to RRP as a method of local, and potentially curative, therapy. Furthermore, prostate cancers are being detected earlier, before becoming clinically palpable on digital rectal examination, because of PSA testing. This allows for earlier diagnosis, more therapeutic options, and better patient selection for surgical therapy. In Croatia, PSA testing was introduced in early 90s and the use of RRP systematically begun at our department in the middle 1990s, before most urological centres. From 1994 to 1996 only few RRPs were performed, and before that all patients with localized disease were treated with hormonal therapy, surgical castration or watchful waiting (careful observation with intention to treat). At our centre there was a dramatic increase in the number of procedures, from 1996 to 2000, followed by a more stabilising trend in 2003, 2004 and 2005. Today, the annual RRP rate is over 150. The dramatic increase in the number of procedures over the study period was caused mainly by an introduction and popularisation of serum PSA testing to the community and primary health care providers. The reason for the relative stabilisation in RRP rate in the past few years is less certain than the dramatic increase, but it may reflect the decreasing incidence of prostate cancer that has been attributed to the depletion of the prevalent pool of undiagnosed cancers[14,15].

In contrast to the findings of Stamey et al and Moul et al, our results showed an annual trend of increasing age

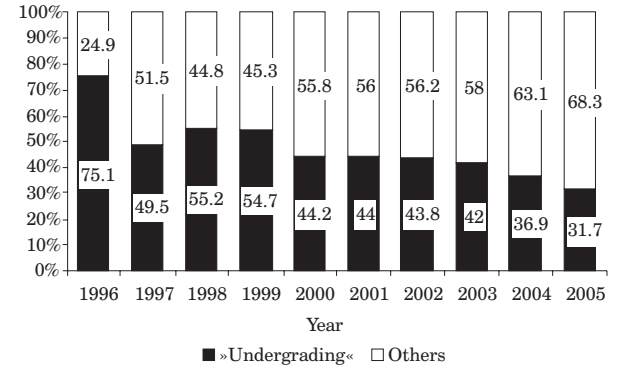

Fig. 10. The annual trends in proportion of patients who were »undergraded«.

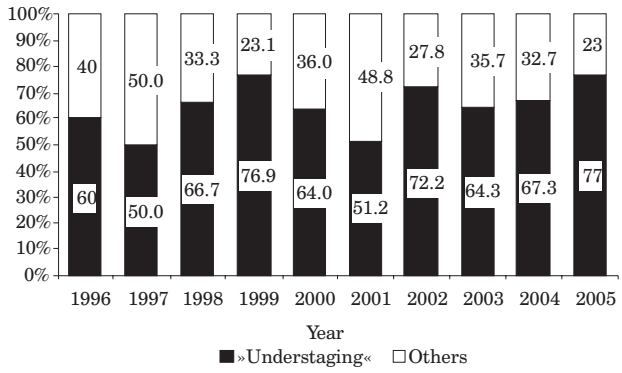

Fig. 11. The annual trends in proportion of patients who were »understaged«.

at surgery[16,17] Furthermore, the percentage of men aged more than or equal to 70 years old increased from 12.5% in 1996 to 26.5% by 2005. Similar trend was observed in other studies[18–20]. It is mainly because our patient selection criteria extended over the age 70 years due to more recently increased life expectancy of men in Croatia.

PSA is the most important preoperative selection and staging tool followed by biopsy Gleason grade and clinical stage. Studies from leading institutions with a large number of RRPs recommend reduction of preoperative PSA levels. The PSA level at the time of diagnosis is a general surrogate for tumor volume or burden, and Figure 4 documents the marked shift to lower PSA values over time in our institution. Mean preoperative PSA value has gradually decreased in the study period, but there was an increase in percentage of patients with pretreatment PSA values ranging from 4.0 to 10.0 ng/mL (Figure 5) which reflects an advancement in patient selection criteria for RRP over the years. Similarly, men with a PSA value >20 ng/mL are at high risk of surgically incurable disease, and this group declined from 30.1% in 1995 to 4.2% by 2005.

As to the selection of patients by clinical staging, the absolute contributions of cT1c disease (detected by an elevated PSA level only and prostate biopsy afterwards) have steadily increased and accounted for 70% of all cases in 2005. By the same token, the proportion of patients with palpable disease (T2) declined from 74.5% in 1995 to only 30% by 2005. The dramatic increase in PSA-detected, nonpalpable, or clinical T1c disease has been documented in other series. Most notably, Arai et al. documented that T1c disease increased from 13.9% to 37.9% between 1991 and 1998 in a combined series of 7 centres in Japan including 638 patients[21]. Similarly, Stamey et al. found that cT1c disease went from 10% of cases in 1988 to 73% by 1996[16]. The increased use of PSA testing is probably the main contributing factor to the increase in detection rate and proportion of clinical T1c disease[16,22,23]. Repeated TRUS biopsy, better and gentler tissue sampling with eight or more cores per biopsy taken in patients with an initially negative sextant biopsy is an equally important contributing factor. Traditionally, six core TRUS guided biopsies were performed at our department (from 1994 to 1997). The contribution of laterally directed TRUS biopsies with eight and more cores per patient at our institution increased markedly up to 80% in 2005. A less significant factor might be that fewer patients undergo transurethral resection of the prostate. Overall, there is a significant decrease in incidental carcinomas in higher stages.

With the advent of PSA testing many countries have seen a significant clinical and pathological stage migration toward organ-confined disease, such is in our case[18–25]. On final pathological staging, the proportion of patients with pathologically organ confined disease increased remarkably during study period from 25% in 1996 to 74.7% in 2005. Similarly, our colleagues from Graz in Austria reported the rates of postoperative organ-confined disease increasing from 47% in 1993 to 79% in 2004[26]. In their centre, the annual frequency of RRPs increased from 43 in 1994 to 160 in 2004, which is comparable to our results[26].

Radical prostatectomy is a demanding urological operation. A key indicator of the quality of a surgical resection is the incidence of positive surgical margins in patients with organ-confined cancer. The surgical technique must be the most precise and rigorous possible because positive surgical margins expose the patient to a risk of disease recurrence directly related to the surgical procedure. The margin positivity in our study decreased from 49.4 % in 1996 to 25% in 2005. This is somewhat higher than in other RRP series, although evaluation of the CaPSURE data base with patients recruited from 29 mainly community and some academic urology practice sites reveals a positive surgical margin rate of 34% with 6% of pathological reports indeterminate[18,19,27].

There were also significant annual changes in the proportion of percent preoperative Gleason grade 5, 7 and 8 cancer, with proportion of Gleason grades 7 and 8 increasing and proportion of Gleason grades 4 and 5 decreasing over a 10-year period which indicates tendency of the pathologist to assign a higher primary Gleason grade in prostate biopsy specimens, so there is significant decline in undergrading over the study period. More accurate grading can be also explained by a decreasing percentage of patients who have received neoadjuvant therapy prior to surgery (from 78.5% in 1996 to 5.4% in 2005). The rates of patients who were understaged have remained relatively stable over the years as seen on Figure 11.

During the observation period, there is a marked annual increase in RRP rate with an increasing contribution of nonpalpable cancers, diagnosed solely on pathological PSA levels (as indication for prostate biopsy). The increase in the number of RRPs during the past decade might be a result of the improved detection rate rather than a real increase in incidence among Croatian men. An increase in the rate of surgical interventions is also a result of continuing education of urologists, exchange of ideas, published technical improvements in the surgical procedure, and other factors, ultimately benefiting the patient by improving outcomes[28]. Also, an increase in organ-confined disease in patients undergoing RRP might be biased by better and more rigorous patient selection. Specifically, a greater proportion of low-risk patients may be selected for RRP. On the other hand, higher risk patients may ultimately choose external beam radiotherapy over RRP. Overall, there was a trend toward more favourable outcomes for pathological variables (an increased percentage of organ confined disease, decreased margin positivity, decreased understaging and a decreased incidence of positive lymph node metastasis on frozen section analysis). These data are the result of careful patient selection for surgery, progressive refinement of operative technique and improvements in perioperative management at our department.

Conclusions

The RRP remains the procedure of choice for the cure of localized PC in patients with long life expectancy and good overall status. As seen from our data during the 10-year period, PC was increasingly detected on the basis of a pathological PSA level only and shifted significantly to more organ-confined stages due to a more accurate assessment of clinical stage prior to surgery, reduced patient morbidity, reduced use of neoadjuvant therapy and improved surgical technique. With a time delay, these findings are consistent with trends observed at several well-known academic institutions in the region and in the USA[26,29–31]. Our data also argue strongly that current PSA testing has resulted in the detection of clinically more organ confined cancers, and that PSA testing and routine DRE should be expanded and not restricted.

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POBOLJAŠANJE KLINIČKE SLIKE I ISHODA NAKON RADIKALNE PROSTATEKTOMIJE U BOLESNIKA S LOKALIZIRANIM KARCINOMOM PROSTATE – PROMJENE U DESETOGODIŠNJEM RAZDOBLJU

SAŽETAK

U radu prikazujemo promjene kliničke slike i ishoda nakon radikalne retropubične prostatektomije (RRP) u bolesnika s lokaliziranim karcinomom prostate tretiranih na našem odjelu, naglašavajući epidemiološki značaj kretanja u razdoblju od deset godina. Analizirali smo godišnje promjene dobi bolesnika, preoperativnih vrijednosti prostata specifičnog antigena (PSA), preoperativnih i postoperativnih stadija i gradusa tumora, statusa lokaliziranosti tumora i statusa kirurških rubova. Od siječnja 1996 do studenog 2005 učinjeno je 488 zahvata, s godišnim porastom od 8 do 129 (1512,5%). Prosječna dob bolesnika porasla je od 61,5 u 1996 do 66,12 godina u 2005, uz istovremeni porast udjela bolesnika starijih od 70 godina od 12,5 do 26,5 % u istom razdoblju. Udio bolesnika u kojih je detektiran karcinom prostate samo na osnovi patoloških vijednosti PSA (kao indikacije za biopsiju prostate) porastao je impresivno od 25,5 do 70 % u 2005, uz istovremeni porast udjela postoperativno lokalizirane bolesti od 25 do 74%. Prosječna godišnja vrijednost preoperativnog PSA smanjila se sa 16,7 na 8,9 ng/mL. S druge strane bilježimo porast udjela bolesnika s rasponom preoperativnih vrijednosti PSA između 4 i 10 ng/mL (od 20 u 1996 do 65,4% u 2005). Stope pozitivnih kirurških rubova smanjile su se od 49,4 do 25% u ispitivanom razdoblju. Udio bolesnika koji su primali neoadjuvantnu terapiju smanio se sa 78,5 na 5,4%. Udio bolesnika u kojih je bio podcijenjen gradus tumora smanjio se sa 75,1 na 31,7%. Stope podcjene stadija ostale su relativno stabilne tijekom godina. U ispitivanom razdoblju sve više je karcinoma detektirano biopsijom prostate samo na osnovi povišenih vrijednosti PSA, te postoji značajna migracija stadija ka lokaliziranoj bolesti. Ovo je rezultat šire primjene PSA, točnije procjene preoperativnog stadija, pooštravanja kriterija pri selekciji pacijenata pogodnih za operativni zahvat, te poboljšanja kirurške tehnike. Naši rezultati sugeriraju da bi rutinsko PSA testiranje trebalo biti stimulirano, a ne ograničavano.