Impact on Prostate Cancer Clinical Presentation After Non-Screening Policies at a Tertiary-Care Medical Center.

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Abstract

BACKGROUND:

In May 2012 the US Preventive Task Force (USPTF) issued a ‘D’ recommendation for routine PSA-based prostate cancer early detection. This recommendation was implemented progressively in our health system. The aim of this study is to define its impact at a tertiary care institution.

METHODS:

A retrospective analysis was performed from 2012 till 2015 at a single center. We analyzed the total number of biopsies performed per year and the positive biopsy rate. For those patients with positive biopsies we recorded diagnostic PSA, clinical stage, ISUP grade group, nodal involvement and metastatic status at diagnosis.

RESULTS:

A total of 1686 biopsies were analyzed. The positive biopsy rate (PBR) increased from 25% in 2012 to 40% in 2015 ($p<0.05$). No change in median PSA was noticed ($p=0.627$). Biopsies detected higher ISUP grades ($p=0.000$). In addition, newly diagnosed prostate cancer presented higher clinical stage ($p=0.005$), higher metastatic rates ($p=0.03$) and a tendency to higher lymph node involvement although not statistically significant ($p=0.09$).

CONCLUSION:

After the 2012 recommendation, patients presented higher probability of diagnosing prostate cancer, with more adverse ISUP group, clinical stage and metastatic disease.

These results should be considered to implement a risk adapted strategy for prostate cancer screening.

Background

Prostate cancer is the second most commonly diagnosed and the most prevalent cancer among males, with 358 989 worldwide deaths during 2018 (1). Since the introduction of PSA-based prostate cancer screening in the late 1980´s, prostate cancer incidence increased considerably and reductions up to 50% in mortality were reported (2–6). However, the increased diagnosis also portends an increased overdiagnosis and overtreatment (7–9) with its related complications (mainly anxiety, sepsis, urinary incontinence and erectile dysfunction) (10–12). The risk/benefit of prostate cancer screening became controversial and still is.

In May 2012 the US Preventive Task Force (USPTF) issued a ‘D’ recommendation for routine PSA-based prostate cancer early detection, stating that it shouldn´t be offered in the general U.S. population, regardless of age (13). This recommendation was based on the results of two randomized trials willing to

prove if screening could reduce prostate cancer mortality. The “Prostate, Lung, Colorectal, and Ovarian (PLCO)” screening trial, in which 76 685 men between 55–74 years were randomized to either annual PSA screening and digital rectal examination for 6 years or ‘usual care’ showed no mortality advantage at 10 years follow up (RR of 1.11 [CI, 0.75 to 1.70]) (14). Longer follow up in the PLCO still fails to prove benefit for screening (RR of 1.04 [95% CI, 0.87–1.24]) at 15 years (15). The European trial (ERSPC) randomized 182 160 men between the ages of 50 and 74 years and found a statistically significant 21% reduction in prostate cancer mortality in men between 55 and 69 years (RR of 0.79; [CI, 0.68 to 0.91; P = 0.00]) at 11 years follow up (16). The aim of this study is to analyze the 2012 recommendation impact at our institution.

Methods

After obtaining institutional ethics committee approval we conducted a retrospective review of all patients who underwent prostate needle biopsies (PNB) at a single tertiary-care institution between January 2012 and December 2015. Patients were excluded from the analysis if they had been previously diagnosed with prostate cancer or had prostatic intraepithelial neoplasia (PIN) or atypical small acinar proliferation (ASAP) in the absence of any prostatic adenocarcinoma. We analyzed the total number of biopsies performed per year and the positive biopsy rate. For those patients with positive biopsies we recorded diagnostic PSA, digital rectal examination (DRE), ISUP grade group, nodal involvement and metastatic status. Chi square test of independence was used to compare positive biopsy rates, Mann-Whitney U test was used to compare prebiopsy PSA and Chi square Mantel-Haenszel test (linear by linear) for temporal tendency in the rest of the variables. Statistical significance was set at a p value < 0.05. Analysis was performed with SPSS 23.0 version.

Results

During the studied period 1 686 prostatic needle biopsies were performed. An overall 45% reduction was observed in the number of biopsies performed between the first and last year studied. Table 1 shows the total number of biopsies and the positivity rate per year. The percentage of positive biopsies were 25% in 2012, 24% in 2013, 38% in 2014 and 40% in 2015, representing a significant increase ($p < 0.0001$).

The clinical presentation based on the digital rectal examination (DRE), the ISUP grade and the distant metastasis was significantly worse in the later years studied. The lymph node involvement showed a non statistically significant increase and the PSA value at diagnosis did not show any difference along the study period.

The proportion of clinical stage T1 and ≥ T3 were 63,3% and 8,0% in 2012, 62,8% and 11,5% in 2013, 58,6% and 14,1% in 2014 51,6% and 18,8% in 2015 respectively ($p = 0.005$). Figure 2 summarizes the ISUP distribution per year. A significant higher ISUP grade was seen in the temporal trend test linear by linear ($p = 0.000$).

Significant differences were observed in distant metastasis at diagnosis (linear by linear chi square test p = 0,024) with a proportion of 8,8%, 11,2%, 9,3% and 18,6% each year (Fig. 3). An increasing trend in lymph node involvement was observed with a proportion of 10,8%, 13,1%, 11,3% and 18,6% yearly. However, these differences did not meet conventional levels of statistical significance (p = 0.09).

Surprisingly, the median PSA was 9,0 ng/dl (ICR:6,1–14,3) for 2012; 9,5 ng/dl (ICR: 6,3–23) for 2013; 8,3 ng/dl (ICR: 5,9–17) for 2014 and 8,3 ng/dl (ICR: 6,01–21) for 2015 (Fig. 4). This difference in PSA values did not show a statistically significant difference (p = 0.627).

Discussion

After the recommendation against massive prostate cancer screening by PSA many studies have shown an increase in the diagnosis of high grade, locally advanced and metastatic prostate cancer (22–24). Our results showed a significant impact of screening policies, with a 45% decrease in the total number of biopsies performed per year and a significant increase in positive biopsy rates between 2012 and 2015. Our results confirm the findings of other groups that found a significant decrease in the median number of biopsies (25, 26) and a 29% increase in positive biopsy rate (26). Contrary to what we expected, our study was not able to show a significant increase in PSA at initial presentation, which was a constant in our examination of the literature (23, 28–30). Although we are not able to give a definite explanation to this finding, we believe it might occur because of different derivation criteria of the associated centers, different level of compliance of the indication not to perform PSA screening and the rising utilization of prebiopsy MRI in the studied period.

We observed a significant increase in local tumoral aggressiveness, mostly because of an increase of the clinical staging cT2-4, and an increase in the ISUP 4 and 5. In their study, Banjeri et al. reported similar findings, with higher clinical stage (cT2b, p = 0.003; cT2c-3a, p = 0.027) and with D´Amico high risk scores (p = 0.036) after the USPTF recommendation (29). We analyzed the histological aggressiveness using the ISUP grading system. Several authors reported their results using the Gleason score and found a significant increase in grade (26, 30, 31). This increase in the diagnostic Gleason score has been also confirmed in radical prostatectomy final pathology (32).

We identified a significant raise in metastatic prostate cancer at the time of initial diagnosis, which in our opinion is the most important negative consequence of the implementation of non-screening recommendations. Our data supports the results described by other authors showing increased incidence of metastatic prostate cancer at time of diagnosis. Bernstein et al., analyzing the SEER database reported that in men ≥ 75 years old, the diagnosis of distant metastases increased in 2012 compared to 2011 (IR 1.13, 95% CI 1.02–1.24, p < 0.05) (33). Using the same database, Hu et al. confirmed this increase between 2010 and 2013 either in men < 75 years (2.7%; 95%CI, 2.5%-2.9% vs 4.0%; 95%CI, 3.8%-4.2%) and > 75 years (6.6%; 95%CI, 6.2%-7.0% vs 12.0%; 95%CI, 11.2%-12.7%) (34). In a population-based data review from 18 SEER registries, Dalela et al. noted that the incidence of metastatic prostate cancer increased significantly between years 2009 and 2013 at a rate of 3.1% per year (P < 0.05) (35).

Interestingly, Weiner et al found that the increase in the annual incidence of metastatic prostate cancer was higher among men aged 55–69 years (36). This is especially bothersome, because this group is the most likely to benefit from definitive treatment. We failed to confirm a significant increase in pelvic lymph node metastasis, although we observed a rising trend such as the result obtained by Blair et al. It is worth noting that these results contrast with those reported by Bernstein et al., who analyzing the SEER database showed a significant increase on pelvic lymph node metastasis between 2004 and 2014 (from 54.1 to 79.5 per million men (IR 1.47, 95% CI 1.33–1.62, $p < 0.01$) (33).

Updated results from de ERSPC trial confirm the risk reduction of developing metastasis (HR: 0.70; 95%CI, 0.60–0.82; $p = 0.001$) and PCa mortality, with lower number of men needed to be invited for screening and to diagnose to prevent a prostate cancer death (570 and 18 respectively) (37, 38). It is important to mention that in a predictive model, discontinuation of screening eliminates all overdiagnoses but more than doubles metastatic cases at presentation and increase 13–20% prostate cancer deaths (39).

Although our study gives important information about the impact of the 2012 recommendation on PSA screening in our population, we are aware of its limitations. In addition to it retrospective design and inherent biases, as a tertiary center with different associated centers we don't know exactly the derivation criteria used, the level of penetration of the recommendation and the exact time of adoption in primary health centers. We also think that the increasing use of prebiopsy MRI could have biased our results.

Conclusions

After the recommendation against PSA screening, the diagnostic profile of prostate cancer has changed in our tertiary care institution, with prostate cancer diagnosed at higher clinical stage, with increased histological aggressiveness and increased risk of metastatic disease. While decreased screening can reduce the diagnosis of indolent cancers and avoid unnecessary treatment, it also may lead to missed opportunities to diagnose prostate cancers when they are lower in grade and stage and may be potentially curable. In this direction different urologic societies are working to provide risk adapted guidelines. This result should be discussed with the patients when counselling for prostate cancer screening.

Abbreviations

PSA prostate specific antigen

DRE digital rectal exam

PIN prostate intraepithelial neoplasia

ASAP atypical small acinar proliferation

PNB prostate needle biopsy

Declarations

Acknowledgements

None.

Authors' contributions

AV, MR and AA have given substantial contributions to the conception or the design of the manuscript, TA, CM and JD to acquisition, analysis and interpretation of the data. All authors have participated to drafting the manuscript, author AA revised it critically. All authors read and approved the final version of the manuscript.

All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

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Availability of data and materials

The data supporting the conclusions used and/or analyzed in this study are available from the corresponding author by request.

Ethics approval and consent to participate

This was a retrospective study approved by the Hospital Clinic of Barcelona ethical committee (CEIm). Informed consent was waived.

Consent for publication

The data do not contain any information that could identify the patient, therefore consent for publication was waived.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Total number of biopsies and positivity rate.

	2012	2013	2014	2015
Positive biopsies	152	118	100	135
Negative biopsies	446	378	163	196
Total number of biopsies	598	496	263	329
Positive biopsy rate (%)	25	24	38	40

Figures

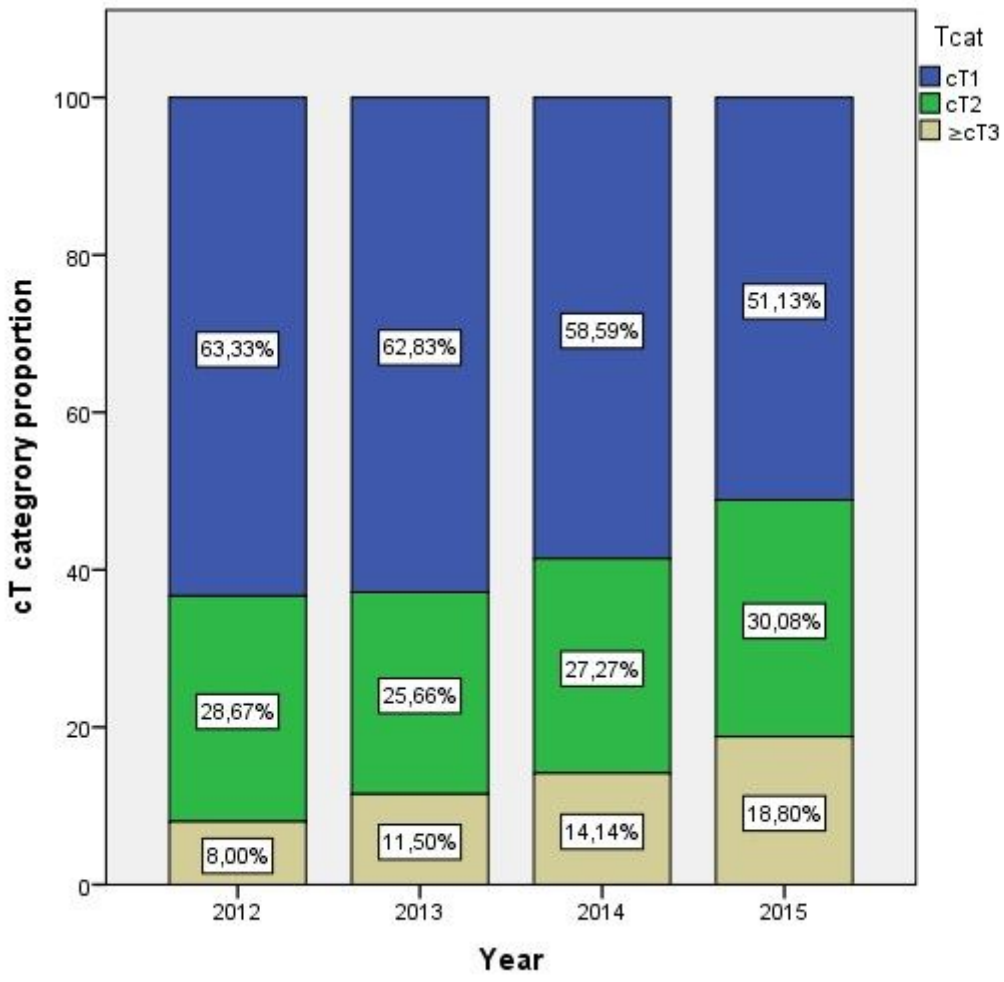
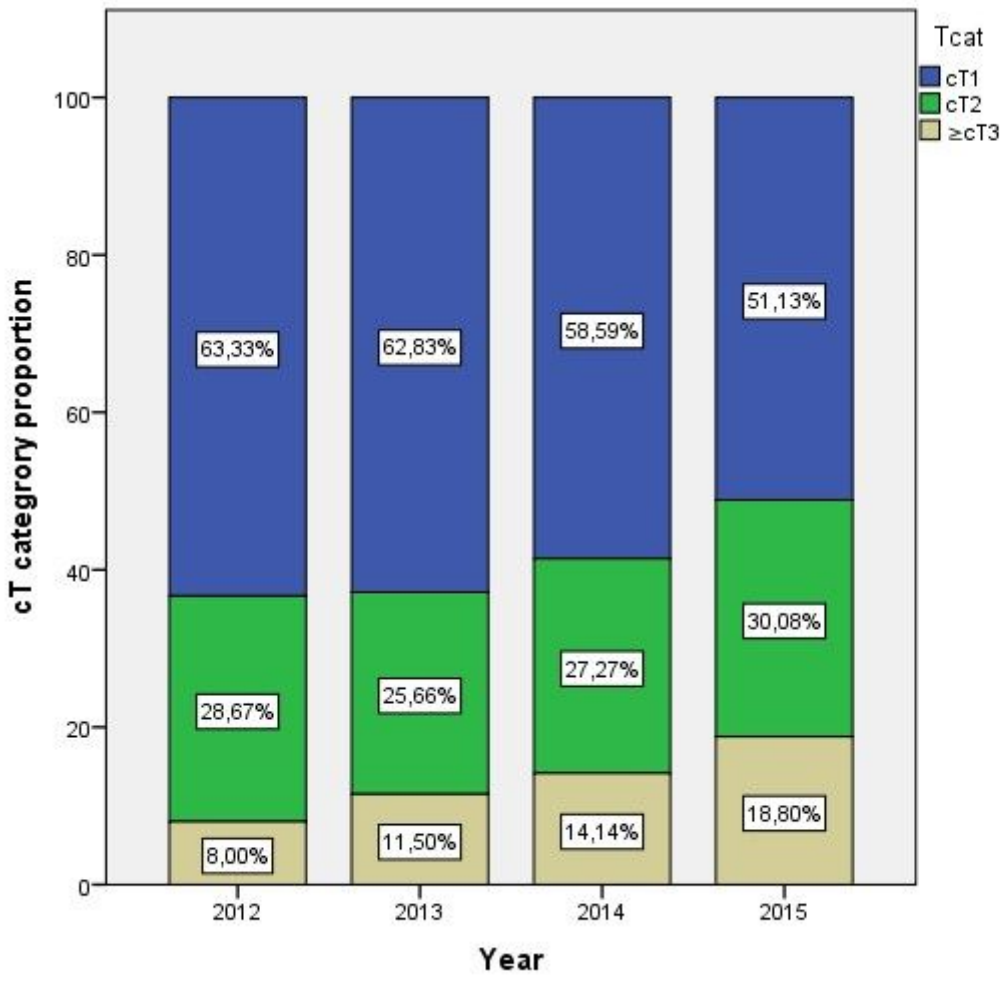


Figure 1

Clinical stage (DRE)/year.



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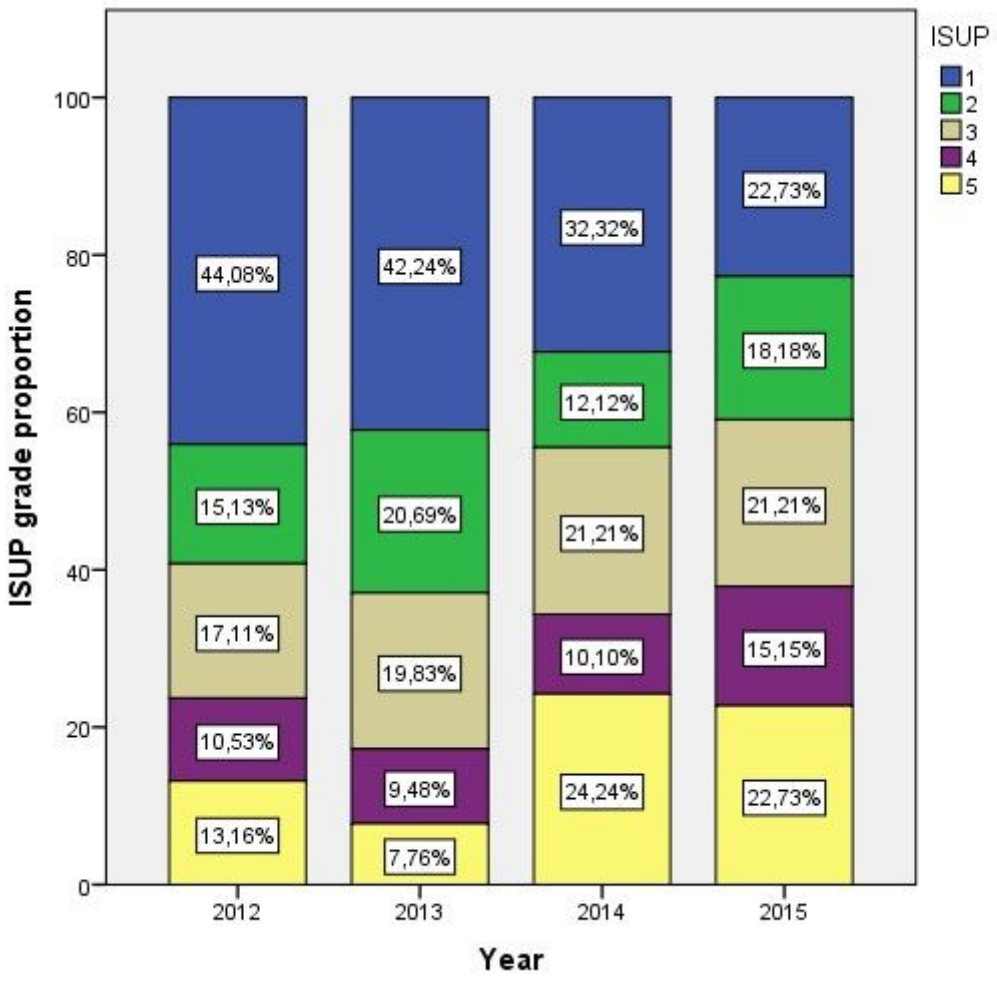
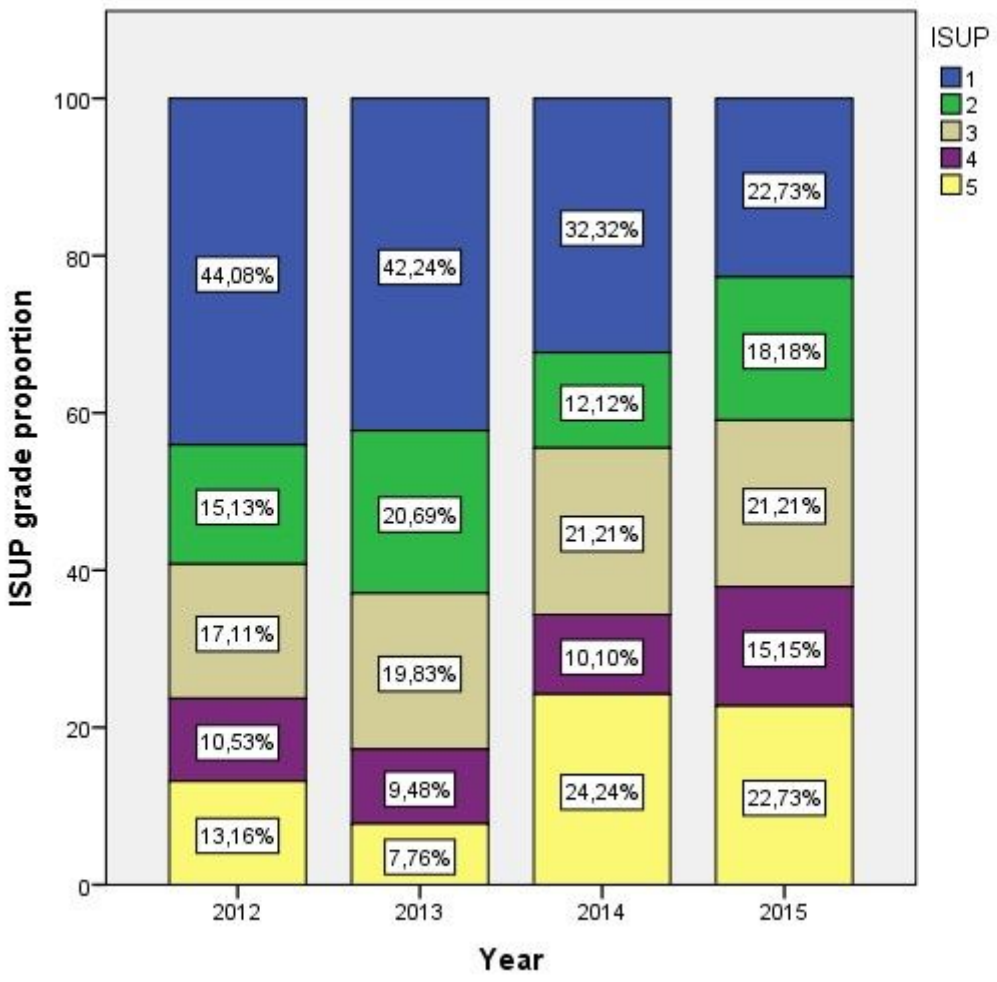


Figure 2

ISUP distribution/year.



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ISUP distribution/year.

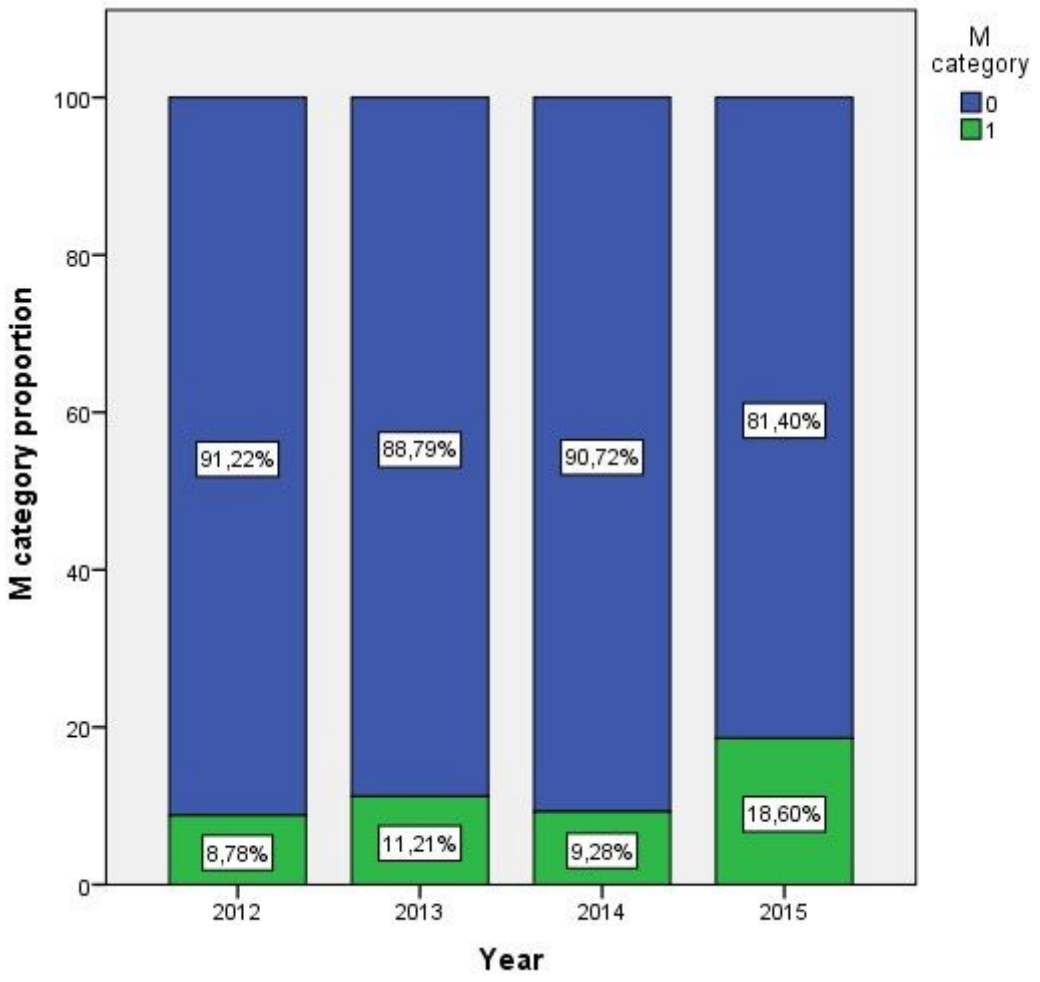
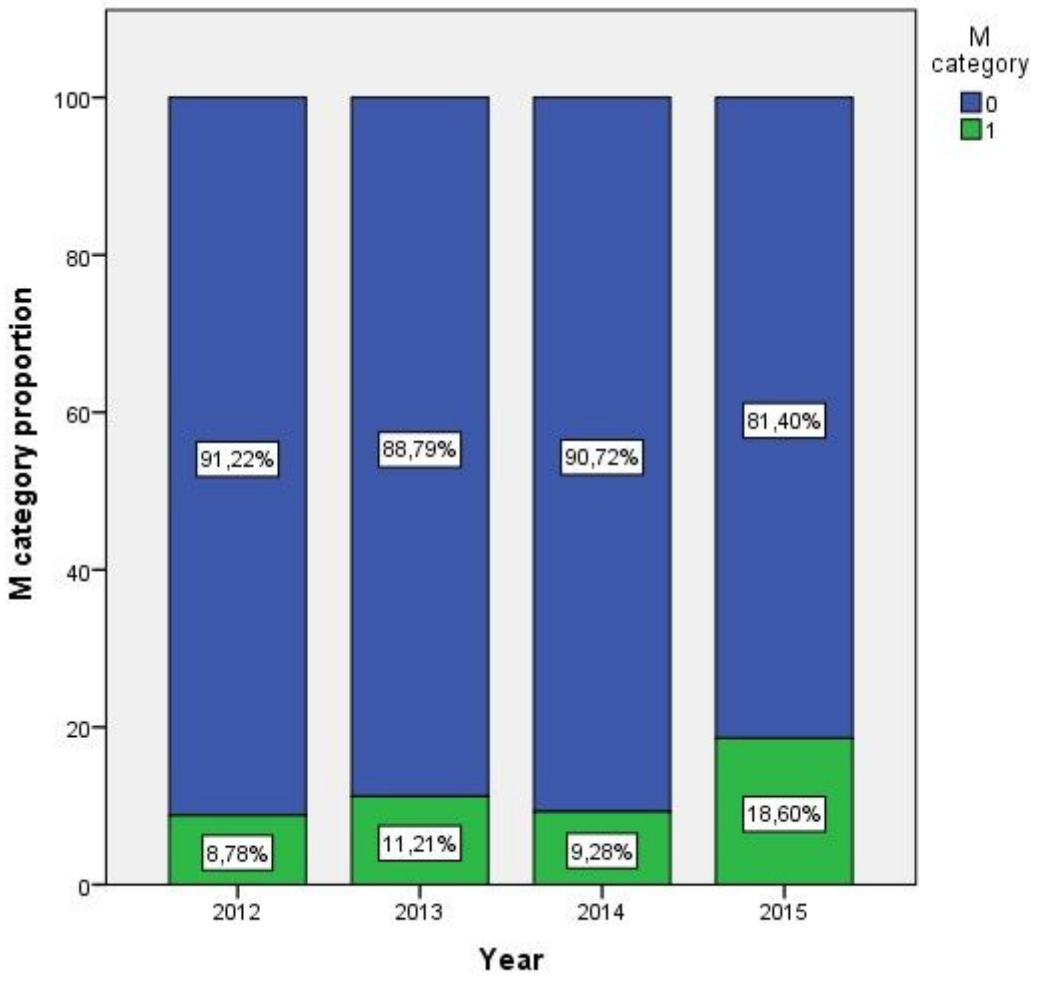


Figure 3

Distant metastasis at diagnosis/year.



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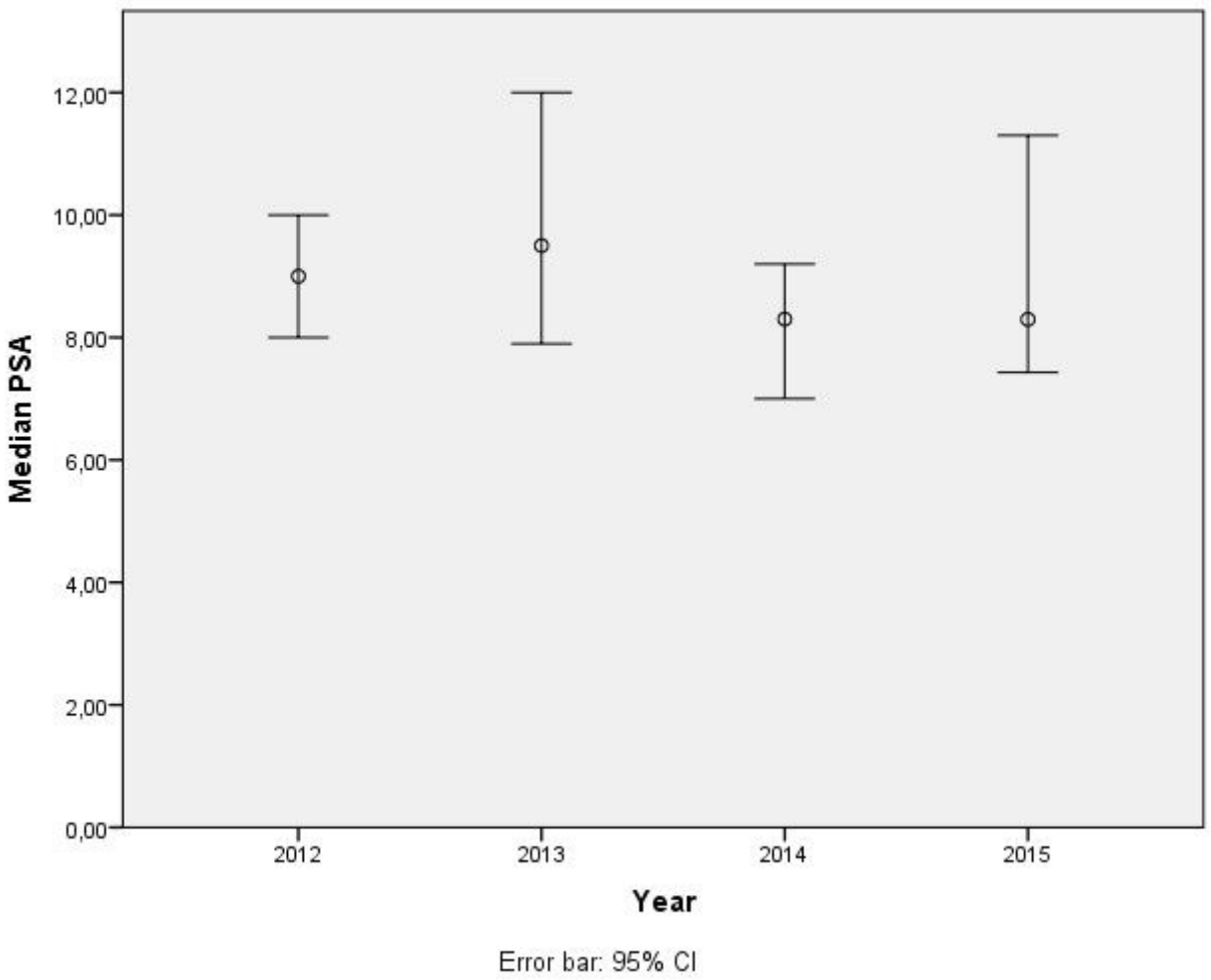
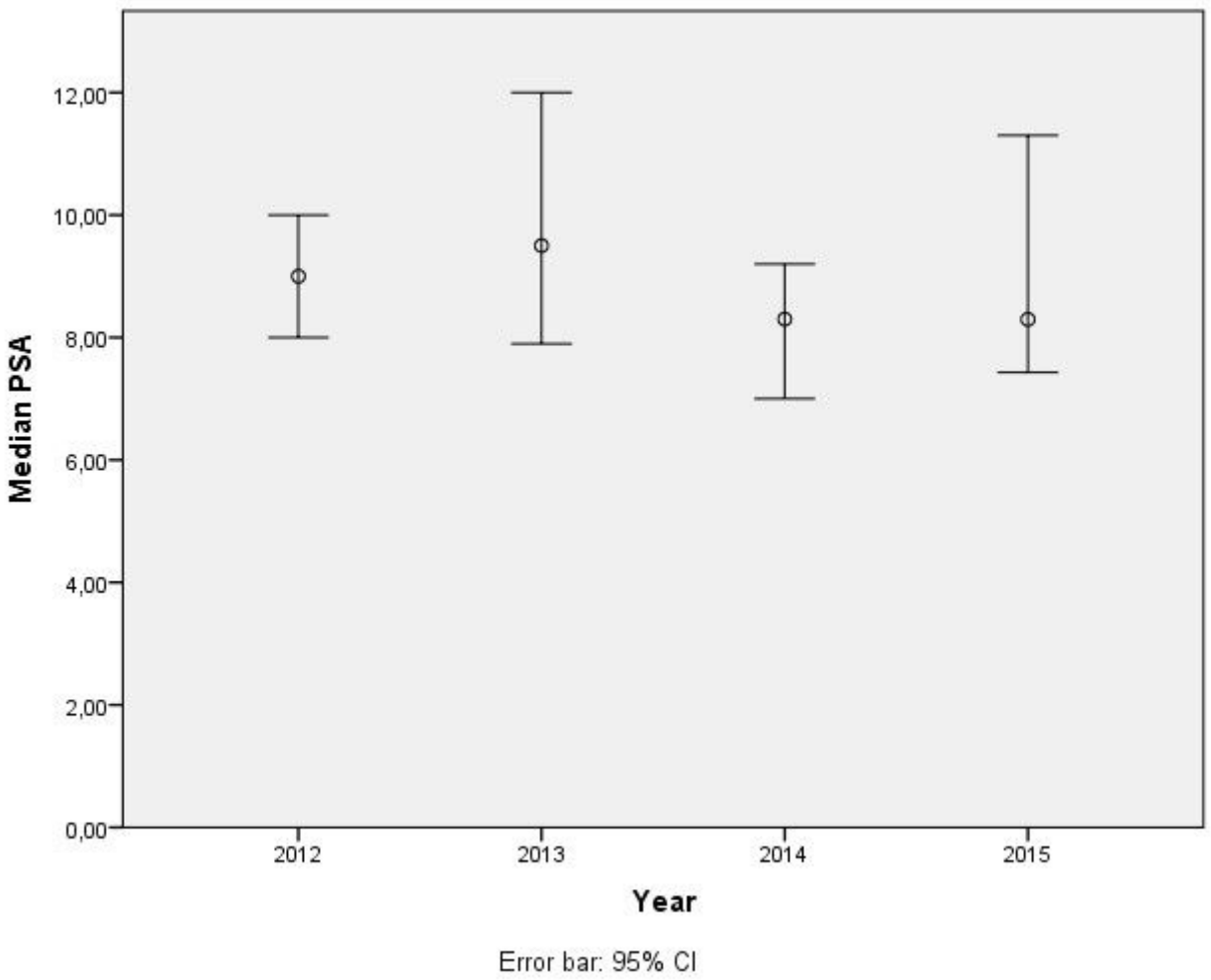


Figure 4

Annual median PSA.



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