A PATIENT-ORIENTED DECISION SUPPORT FRAMEWORK AND ITS APPLICATION TO BIOPSY DECISION FOR PROSTATIC CARCINOMA

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Approval of the Graduate School of Informatics

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ABSTRACT

A PATIENT-ORIENTED DECISION SUPPORT FRAMEWORK AND ITS APPLICATION TO BIOPSY DECISION FOR PROSTATIC CARCINOMA

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Serum PSA (Prostate Specific Antigen) level is used for prediction of prostatic carcinoma, but it suffers from weak sensitivity and specificity. We applied logistic regression, artificial neural networks, decision tree, and genetic algorithm to prostate cancer prediction problem to design a model for Turkish population. A hybrid model of logistic regression and decision tree has been designed. The model could prevent 33 biopsies (4.4% of our patients who have PSA level between 0 and 10) from our data set without a loss from sensitivity. The prepared online decision support tool and a questionnaire were published on a website. Fifty urologists have completed the questionnaire. Cronbach's alpha was 0.770. On a five graded Likert scale, the mean score of "attitude to computer use in healthcare" (ACH) was 4.2. The mean of eight

responses related to the online tool (Attitude to Decision Support Tool; ADST), was 3.7. ADST was correlated with ACH (r=0.351, p=0.013). Physicians who have positive attitude to computer use in healthcare tend to use the tool (r=0.459, p=0.001). The first factor influencing the opinions of the urologists was the attitude of the user to computer use in healthcare, the other factor was the attitude of the user to the decision support tool itself. To increase the acceptance, education and training of physicians in the use of information technologies in healthcare, informing users about the logic of the decision support tool, and redesigning the system according to user feedback may be helpful.

Keywords: Prostate Specific Antigen, Clinical Decision Support Systems, Prostatic Neoplasms, Attitude to Computers, Internet

ÖZ

HASTA YÖNELİMLİ BİR KARAR DESTEK ÇERÇEVESİ VE PROSTAT KARSİNOMUNDA BİYOPSİ KARARINA UYGULANMASI

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Serum PSA (Prostate Specific Antigen) düzeyi, prostat karsinomunun öngörülmesi için kullanılır, ancak, duyarlılık ve özgüllüğü ile ilgili problemler vardır. Bu çalışmada, Türk popülasyonuna uygun bir model tasarlamak için prostat kanserinin öngörülmesi amacı ile lojistik regresyon, yapay sinir ağları, karar ağacı ve genetik algoritma uygulanmıştır. Sonuçta, lojistik regresyon ve karar ağacı kullanılarak hibrid bir model tasarlanmıştır. Bu model, duyarlılıkta bir kayıp olmadan veri setimizdeki 33 hastada biyopsiyi önleyebilmektedir (PSA'sı 10'un altında olan hastaların %4,4'ü). Hazırlanan çevrimiçi karar destek aracı ve bir kullanıcı anketi ile bir web sitesi oluşturuldu. Elli üroloji uzmanı anketi yanıtladı. Cronbach alfa değeri 0.770 hesaplandı. Beş aşamalı Likert skoruna göre "sağlık hizmetinde bilgisayar

kullanımına karşı tutum" (SHBKKT) 4,2'ydi. Çevrimiçi araçla ilgili sekiz sorunun ortalaması ise 3,7 idi (karar destek aracına karşı tutum; KDAKT). SHBKKT ile KDAKT korelasyon göstermekteydi (r=0.351, p=0.013). Sağlık hizmetinde bilgisayar kullanımına karşı tutumu pozitif olan hekimlerin aracı kullanma eğilimi daha fazlaydı (r=0.459, p=0.001). Ürologların araç hakkındaki görüşlerini etkileyen bir faktör sağlık hizmetinde bilgisayar kullanımına karşı tutum, diğer faktör ise aracın kendisine karşı tutumlarıydı. Hekimlerin karar destek sistemlerini kabullenmesini artırmak için sağlık hizmetinde bilgisayarların kullanımı hakkında eğitilmeleri, kullanıcıların karar destek aracının çalışma mantığı hakkında bilgilendirilmeleri ve kullanıcı geribildirimlerine göre araç tasarımının gözden geçirilmesi yararlı olabilir.

Anahtar Kelimeler: Prostat Spesifik Antijen, Klinik Karar Destek Sistemleri, Prostat Neoplazmları, Bilgisayara Karşı Tutum, İnternet

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INTRODUCTION

Some medical decisions in daily practice of medicine have great impact on patient; the result may be life or death. Sometimes, these decisions may not be easy because of complexity of the situation. The physicians usually try to make the decision by simple rules or experience. This approach sometimes causes late diagnose or unnecessary interventions.

The most common malignant tumour is prostatic carcinoma in male (186 320 new cases, 28 660 deaths estimated in USA in 2008) (Jemal, et al.). Luckily, there are some predictors used for early detection of prostatic carcinoma. Serum Prostate Specific Antigen (PSA) level, age, rectal digital examination, and symptoms are helpful for early detection of the tumour (Thompson & Ankerst, 2007).

When the patient is suspected to have prostate tumour, biopsy from prostate is advised by the physician. Sometimes, because of presence of strong indicators, the decision of biopsy is easy. However, sometimes the findings are in grey zone, the physician and patient have to make decision between a risk of missing early detection of the tumour and a risk of unnecessary biopsy (Tricoli, Schoenfeldt, & Conley, 2004). There are several studies which try to establish better approaches to

raise the sensitivity and specificity of the decision in these grey zone patients. The details of these studies will be discussed in next sections.

1.1 Prostatic Carcinoma

Prostate gland is an organ which is found only in man, located near neck of the bladder, around urethra.

Histologically, the prostate gland can be divided into three parts. The peripheral zone forms about 70% of glandular part, and its ducts open into the distal prostatic urethra. The central zone forms about 25% of the glandular prostate, the ducts of which open mainly into the middle prostatic urethra. The transitional zone (about 5%) consists of two small lobes, and the ducts open almost into the sphincteric part of the urethra. The sympathetic nerves control the prostatic musculature, and their excitation closes the bladder neck during ejaculation of the seminal fluid into the urethra. The ejaculate from the human prostate is a slightly acid (pH 6.5), serous fluid in which several major secretory products can be identified, notably acid phosphatase, citrate, zinc, soluble fraction proteins, carbohydrates, electrolytes, polyamines, hormones, lipids and growth factors. Up to 57 major protein groups, of which 27 are non-serum proteins (i.e. presumably exuded by the epithelial cells) have been identified. Major prostatic-specific proteins are prostatic acid phosphatase (PAP), PSA and prostate binding protein (PBP), which are expressed at pubertal and adult ages. Proteolysis is the major function of prostate secretion, being rich in exopeptidase and endopeptidase. The most extensively studied protease is PSA, also known as seminin, seminal protease or chymotrypsin-like protease (Mehik, 2001).

It has three main disturbances; Prostatitis, benign hyperplasia and carcinoma (Epperly & Moore, 2000).

Prostatic carcinoma is the malignant transformation of epithelial tissue of prostate gland. Its incidence rises with advancing age. The enlargement of the gland causes

disturbance in urination. It may be diagnosed because of urinary complaints, or because of a screening test.

Tumours predominantly arise from epithelial cells in the peripheral zone of the gland. Tumours that progress, if untreated, will extend into the prostatic capsule and seminal vesicles, and will ultimately metastasize to regional and distant sites such as lymph nodes and bone. Metastatic hormone-refractory disease is the most important cause of morbidity, treatment failure, and subsequent mortality from prostate cancer (Mora, et al.).

Prostatic intraepithelial neoplasia (PIN) refers to morphological appearances within a spectrum extending between histologically "normal" and "frankly malignant" prostatic epithelium (Park, Shinohara, Grossfeld, & Carroll, 2001). PIN is divided into two grades, low and high (which replaces the previous categories of PIN1 (low grade), PIN2, and PIN3 (high grade). The importance of diagnosing PIN is that high-grade PIN is associated with the presence of synchronous prostate cancer in greater than 35% of cases (Sakr & Partin, 2001).

Its incidence changes according to geographical distribution (Figure 1), and an estimated one in 10 men develop this malignancy at some point in life in USA (Epperly & Moore, 2000).

Despite the frequency of prostate cancer, screening programs remain controversial because of inconclusive evidence demonstrating improved outcomes in patients diagnosed at an earlier disease stage. Use of the prostatic specific antigen (PSA) test for prostate cancer screening is one of the most controversial issues in disease prevention. Conflicting screening recommendations have been presented by various organization and associations (Naitoh, Zeiner, & Dekernion, 1998).

Risk factors for prostate cancer include family history and black race. The presence of benign prostatic hyperplasia is not considered to be a significant risk factor. Smoking and dietary habits do not seem to contribute to the incidence of this cancer. Although early reports showed a slight increase in the incidence of prostate cancer

among men who had vasectomies, current data do not support a causal relationship (Bernal-Delgado, Latour-Perez, Pradas-Arnal, & Gomez-Lopez, 1998).

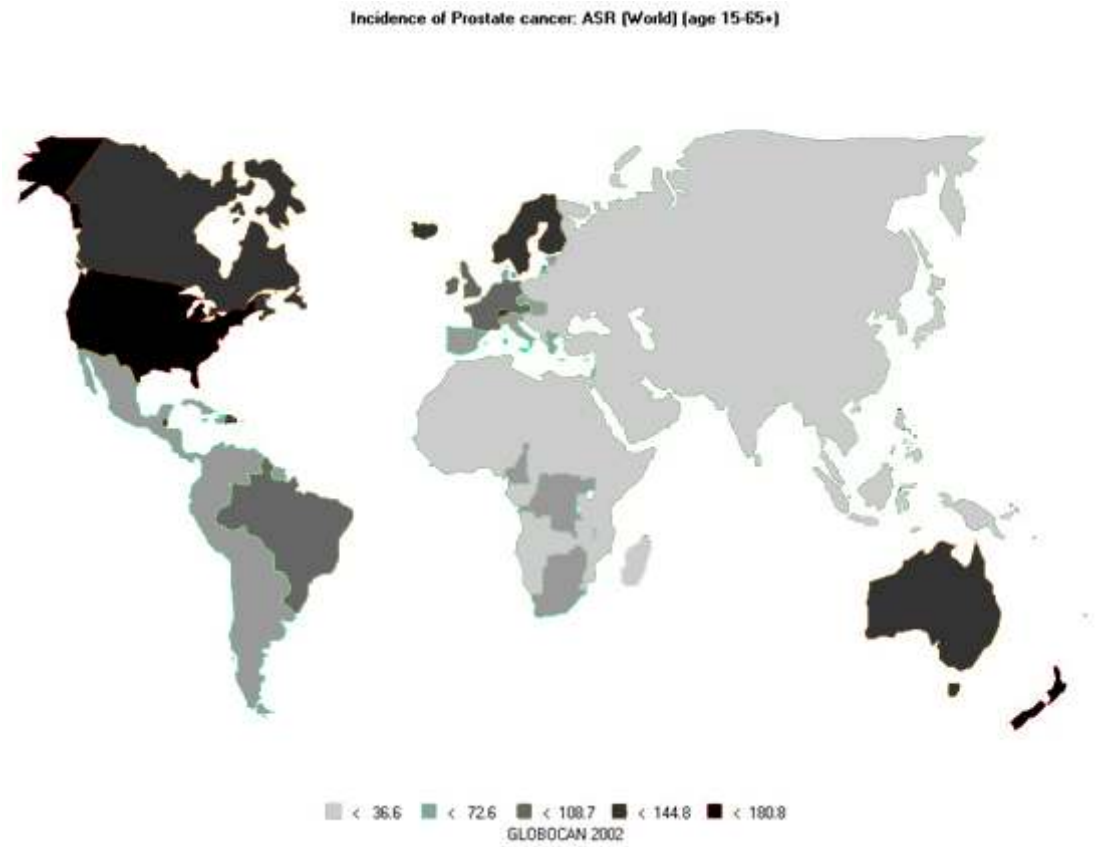

Figure 1: Prostate Cancer Incidence Map (per 100.000)(Group, 2000).

Prostate cancer is an indolent disease in most men. Well-differentiated prostate cancer has a five-year survival rate approaching 98 percent and a 15-year survival rate approaching 83 percent. Conversely, poorly differentiated forms of this cancer have only a 68 percent five-year survival rate and a 25 percent 15-year survival rate. Unfortunately, men diagnosed with prostate cancer before the age of 65 have a higher likelihood of metastatic disease and subsequently poorer outcomes (Epperly & Moore, 2000).

1.2 Physical Examination of the Prostate

An assessment of the size, shape, and consistency of the prostate is an important step in screening for prostate cancer. Because the prostate is located deep within the body, and cannot be seen or felt from the outside, a physician must examine the prostate manually with a digital rectal examination (DRE).

The purpose of the DRE is to identify lesions within the rectum and the prostate. It is the most widely used and oldest technique for the detection of prostate cancer and is used in screening for colon cancer and for the detection of rectal polyps.

Usually the patient is positioned on the left side with the knees close to the chest. Sometimes the patient is asked to stand up and lean over the examination table. After lubricating the gloved finger and anus, the examiner gently slides the finger into the anus and follows the contours of the rectum (Figure 2). The examiner notes the tone of the anus and feels the walls and the edges for texture, tenderness and masses as far as the examining finger can reach. The examiner evaluates the prostate for nodules and tenderness. The examination takes less than two minutes and can be uncomfortable when the patient is not relaxed or is anxious (Branche, 2002).

DRE is a less effective screening tool than the PSA blood test, but it can sometimes detect cancers in men with a normal PSA level. All men over age 50 should have a DRE at least once a year. Men at high risk for prostate cancer—blacks or those with two first-degree relatives (brother or father) with the disease—should have an annual DRE beginning at age 45. Most experts agree that a combination of DRE and PSA screening is the most reliable method for early cancer detection. An abnormal physical examination and high PSA level are usually accepted as indication for biopsy (Grubb, Roehl, Antenor, & Catalona, 2005).

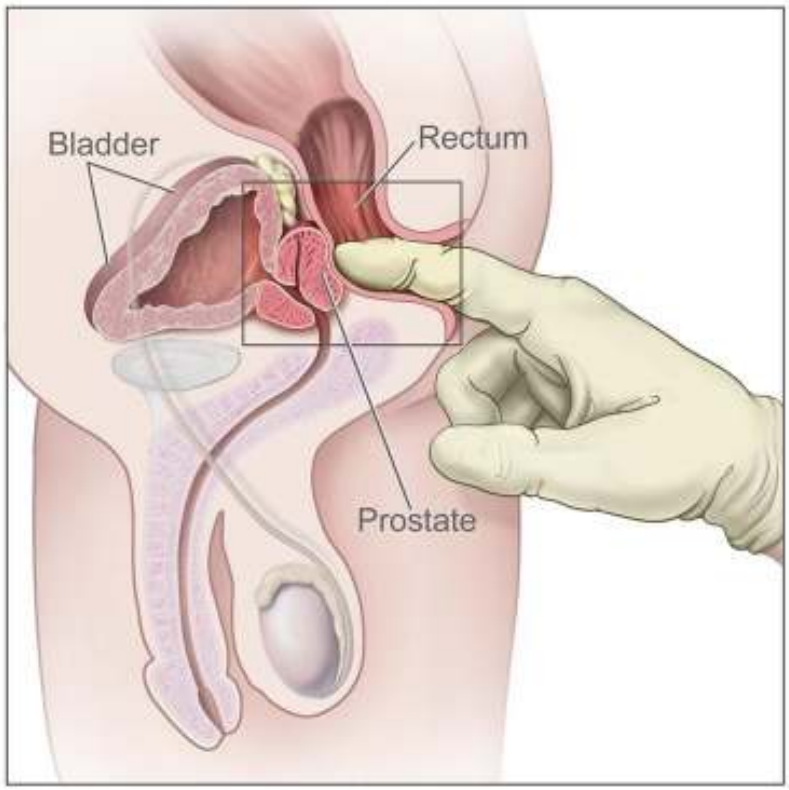

Figure 2: Digital rectal examination (Image source: National Cancer Institute; www.cancer.gov)

1.3 Prostatic Acid Phosphatase

The first documented case of prostate cancer was reported by Langstaff in 1817. One hundred eighteen years later, in 1935, prostatic acid phosphatase (PAP) levels were identified in the ejaculate of men, thus linking this enzyme to the prostate. Subsequent studies showed high PAP concentrations in primary and metastatic prostate cancer tissues and in human serum, making it the first candidate marker for the diagnosis of prostate cancer (Tricoli, et al., 2004). Reductions in serum PAP levels were found to occur in response to antiandrogen therapy, whereas increasing serum levels were associated with treatment failure and relapse (Schacht, Garnett, & Grayhack, 1984). However, whereas serum PAP levels were elevated in a significant number of men with metastatic disease, fewer than 20% of men with localized

prostate cancer exhibited abnormal enzyme levels. Meticulous sample collection and preparation were required because both platelets and leukocytes are contaminating sources of acid phosphatases and because PAP activity is rapidly lost at room temperature (Tricoli, et al., 2004). Development of a radioimmune assay for PAP in 1975 provided some improvement in test sensitivity (Foti, Cooper, Herschman, & Malvaez, 1977), but the sensitivity levels were still inadequate for detection of early-stage disease. Therefore, it was clear that a more sensitive and robust indicator of disease presence would be required to detect prostate cancer in its earlier stages, when cure is more likely.

1.4 PSA as a Marker of Prostatic Carcinoma

It is found in serum of the patient and can easily be measured by routine biochemical methods. PSA is a kallekrein-like serine protease that was first described in 1971(Hara, Koyanagi, Inoue, & Fukuyama, 1971). PSA is secreted from prostate epithelial cells and encoded by an androgen-responsive gene located on chromosome 19q13.3–13.4 (Riegman, et al., 1989). PSA was initially thought to be a prostate-specific protein; however, subsequent investigations demonstrated that PSA is secreted in small quantities from a number of other normal or tumoural male tissues and even some female tissues (Cunha, Weigle, Kiessling, Bachmann, & Rieber, 2006; Gülkesen, et al., 1999). PSA was first detected in the serum of prostate cancer patients in 1980, and a normal PSA serum concentration limit of 4 ng/ml for men was subsequently established. A serum level above 4 ng/ml was taken as an indicator of the possible presence of prostate cancer and served as the trigger for further clinical evaluation. Eventually, a number of studies enrolling large numbers of men over the age of 50 years suggested that quantitation of serum PSA was a useful diagnostic tool for detecting the presence of prostate cancer, particularly when combined with DRE (Catalona, et al., 1991; Labrie, et al., 1992). However, other studies have called into question the sensitivity and specificity of the PSA test (Guinan, Bhatti, & Ray, 1987; Stamey, et al., 1987; Wang & Kawaguchi, 1986).

In men with a normal DRE, if serum PSA is 2.5-4.0 ng/ml, probability of cancer is 10-20%. The probability rises to 25% when the level is 4.1-10. Over 10 ng/ml, 50-60% of the patients have prostatic carcinoma (Schmid, Riesen, & Prikler, 2004). Overall sensitivity is 70-80% and specificity is 70% (Roscigno, et al., 2004).

One problem is that serum PSA levels can be elevated as a result of conditions other than prostate cancer, such as benign prostatic hypertrophy (BPH) and prostatitis. As a result, false positives are a significant problem for the PSA test and can lead to unnecessary biopsies and other interventions. Of greater concern, 20–30% of men with prostate cancer have serum PSA levels in the normal range, resulting in undiagnosed disease (Catalona, et al., 1991; Labrie, et al., 1992). A recent study has concluded that preoperative serum PSA levels do not correlate with cancer volume or the Gleason grade of radical prostatectomy specimens (Stamey, Johnstone, McNeal, Lu, & Yemoto, 2002). This study also showed a poor correlation between preoperative serum PSA levels in the 2–9 ng/ml range and prostate cancer cure rates. Despite the drawbacks and criticisms cited here, PSA is currently the best clinical marker available for prostate cancer and the only one approved by the United States Food and Drug Administration for both posttreatment monitoring of disease recurrence and, when combined with DRE, evaluation of asymptomatic men (Tricoli, et al., 2004).

Age-adjusted ranges for PSA appears to be the more useful, since this enhances cancer detection in younger patients, who benefit most from early diagnosis and treatment, and decreases the number of biopsies performed in older men, who are at less risk of dying from prostate cancer (Richardson & Oesterling, 1997).

1.5 Concepts for Improving the Specificity of PSA

Since 1989, several concepts to further improve the diagnostic accuracy of PSA have been developed with the aim of avoiding unnecessary biopsies. These can be divided into static and dynamic concepts (Table 1). Those in the static group apply at a single

timepoint whereas the dynamic approaches depend on follow up of the patient with serial PSA determinations (i.e. more than one timepoint) (Schmid, et al., 2004).

Table 1: Concepts for improving the specificity of prostate-specific antigen (PSA)

Concept
Static
PSA density
PSA density of transition zone
Age specific reference ranges
Ratio of free/total PSA
Complexed PSA
Izoenzymes free PSA
Dynamic
PSA velocity
PSA doubling time

1.5.1 PSA Density

The oldest concept is PSA density (PSAD) which is determined by dividing the serum PSA level by the volume of the entire prostatic gland as measured by transrectal ultrasonography (TRUS) (Babaian, Fritsche, & Evans, 1990; Benson, Whang, Olsson, McMahon, & Cooner, 1992; Veneziano, et al., 1990). Since cancerous tissue may secrete up to 12 times more PSA per volume of tissue into the serum than benign hyperplastic tissue, PSAD should be higher in cancer patients and

its use should achieve higher specificity than PSA alone. However, the use of PSAD in daily practice is hampered by several factors. Determination of prostate volume by TRUS is largely operator dependent and may vary considerably. Additionally, TRUS is not always available, and is time-consuming and relatively expensive. PSAD can also give false positive results due to subclinical prostatitis and infarction. Finally, where there is concomitant BPH, there may be a "dilution effect" leading to falsely low values.

1.5.2 PSA Density of Transition Zone

A further development of the density idea is PSA density of the transition zone (PSAT). In men with lower urinary tract symptoms and serum PSA values below 10 ng/ml, PSAT is superior to PSAD with respect to diagnostic accuracy (Kalish, Cooner, & Graham, 1994). Problems with PSAT occur most often in small prostates because identification of the transition zone with TRUS is sometimes difficult in these cases. Furthermore, a small gland contains less BPH (low volume of transition zone) and consequently the value for PSAT tends to be higher and the difference between benign and malignant prostatic tissue less clear.

1.5.3 Age Specific Reference Ranges

In a community-based study of healthy men it was found that serum PSA levels were directly correlated to patient age and volume of the prostate, the latter also being directly related to age (Oesterling, et al., 1993). The authors therefore established age specific reference ranges for PSA with the expectation that use of these should increase test sensitivity in younger men and improve its specificity in older men. For a healthy 60-year-old man with no evidence of prostate cancer, the serum PSA concentration increases by approximately 3.2% per year (0.04 ng/mL per year). The recommended reference range for serum PSA (95th percentile) for men aged 40 to 49 years is 0.0 to 2.5 ng/ml; for 50 to 59 years, 0.0 to 3.5 ng/ml; 60 to 69 years, 0.0 to

4.5 ng/ml; and 70 to 79 years, 0.0 to 6.5 ng/ml. This concept is easily applicable in routine practice, but has been criticised because it is likely to lead to a certain number of unnecessary biopsies in younger men and a few cancers will be missed in older men. Until now, there is no study proving the effectiveness of prostatic biopsies using age specific reference ranges below 4 ng/ml (Schmid, et al., 2004).

Müezzinoğlu et al studied the PSA population standards of a cluster of Turkish men with no clinical evidence of prostate cancer. Two hundred fifty-seven men participated in the population-based study. They underwent clinical examination, transrectal ultrasonography and serum PSA measurement. The association between serum PSA and age, prostate volume and age, PSA and prostate volume, and PSA density (PSAD) and age were assessed. Distributions of serum PSA levels, prostate volumes (PV), and PSAD values as a function of age were generated. The upper limit of normal PSA concentration were 4.51 ng/ml for men aged 40-49 years, 4.36 ng/ml for 50-59 years, 6.17 ng/ml for 60-69 years, and 10.18 ng/ml for over 70 years. The upper limit of normal (95th percentile) for the serum PSA concentration increased with age. Across the entire age range, no correlation was found between the serum PSA concentrations and age while significant correlation was found between serum PSA concentration and prostate volume. According to results of this study, PSA values are mainly affected by prostate volume rather than age (Muezzinoglu, Lekili, Eser, Uyanik, & Buyuksu, 2005).

1.5.4 Ratio of free/total PSA

Free PSA (fPSA) is the amount of PSA that is not bound to plasma proteins. Compared with the PSA test alone, the "percent-free PSA" is thought to be more sensitive in identifying patients at risk for prostate cancer. A percent-free PSA of greater than 25 percent is 95 percent sensitive in excluding prostate cancers when PSA values are in the ambiguous range of 4 to 10 ng per ml (4 to 10 µg per L) (Catalona, et al., 1998). In a Turkish study, results for prostates less than 50 ml was

discouraging, areas under the ROC (Receiver Operating Characteristics) curves for percent free PSA, PSAD, and TZPSAD were 0.553, 0.595, and 0.550, respectively (Akduman, Alkibay, Tuncel, & Bozkirli, 2000).

Determination of the free/total ratio can stratify the risk of cancer for men with total PSA levels between 4 and 10 ng/ml and with a negative DRE. In a prospective multicentre trial, prostate cancer was found on biopsy in 56% of men with a ratio less than 0.10 but only in 8% of men with a ratio of more than 0.25 In the multivariate model used, the percentage of free PSA was an independent predictor of prostate cancer (odds ratio [OR], 3.2; 95% confidence interval [CI], 2.5-4.1; $P < .001$) and contributed significantly more than age (OR, 1.2; 95% CI, 0.92-1.55) or total PSA level (OR, 1.0; 95% CI, 0.92-1.11) in subjects with total PSA values between 4.0 and 10.0 ng/ml. Use of the percentage of free PSA can reduce unnecessary biopsies in patients undergoing evaluation for prostate cancer, with a minimal loss in sensitivity in detecting cancer. A cut-off of 25% or less free PSA is recommended for patients with PSA values between 4.0 and 10.0 ng/ml and a palpably benign gland, regardless of patient age or prostate size (Catalona, et al., 1998).

In another prospective trial from a defined geographic area, a significant number of prostate cancer were detected in the total PSA range of 1–3 ng/ml when the free/total ratio was 0.2 or less and the majority of these tumours were clinically relevant (Recker, et al., 2001). Nevertheless, the concept must be interpreted with caution. Several pre-analytical and clinical factors may influence the free/total PSA ratio, e.g. instability of free PSA both at 4 °C and at room temperature, assay characteristics (equimolar versus skewed response), and a "dilution effect" in large prostates due to concomitant BPH, a problem similar to that for PSAD (C. Stephan, Lein, Jung, Schnorr, & Loening, 1997). The free/total ratio is clinically useless in total serum PSA values above 10 ng/ml and in follow up of patients with known prostate cancer.

1.5.5 Complexed PSA

It has been shown that the proportion of circulating complexed PSA is higher in patients with carcinoma than in those with BPH. The determination of various complexed forms of PSA (cPSA) using a blocking antibody to prevent binding of free PSA has been introduced recently (Allard, Zhou, & Yeung, 1998). Studies comparing the diagnostic efficacy of cPSA with total PSA and the free/total PSA ratio report diverging results. Superior performance for cPSA over total PSA or the free/total ratio (Brawer, et al., 1998), superiority of cPSA over total PSA but not over the free/total ratio (Djavan, et al., 2002), equivalency of cPSA with total PSA and the free/total ratio (Lein, et al., 2001), as well as equivalency of cPSA with total PSA but superiority of the free/total ratio over cPSA (Filella, et al., 2000) have all been reported. Analogous to the early experience with the free/total PSA ratio, the performance of cPSA may well depend on the total PSA concentration range investigated and recent studies focus on very narrow and low total PSA ranges, e.g. 2 or 2.5–4 ng/ml (Horninger, et al., 2002). According to one study, cPSA is more cost-effective compared to total PSA or free PSA/tPSA (Ellison, Cheli, Bright, Veltri, & Partin, 2002). The role of cPSA in the diagnosis of prostate cancer still remains to be defined (Rittenhouse & Chan, 1999).

1.5.6 Izoenzymes free PSA

The observation of an irregular intracellular glycosylation process of proteins in dysplastic cells of the prostate prompted researchers to study the microheterogeneity of serum PSA (Huber, et al., 1995). Isoenzymes of free PSA in the sera of patients with BPH were mainly located in the pI (isoelectric point) range of 6.6–7.3, whereas isoenzymes in the sera of prostate cancer patients were mainly in the pI range of 7.0–8.3. These results suggest that PSA isoenzymes released from BPH tissue contain more sialic acid residues than PSA released from cancerous tissue but these experimental observations still require clinical validation.

1.5.7 Dynamic Concepts

An increase of PSA over time can either be expressed as PSA velocity (PSAV) or PSA doubling time (PSADT). PSAV was recommended as a means of enhancing the specificity of PSA for prostate cancer detection (Carter, et al., 1995). PSAV has been defined as an absolute annual increase in serum PSA (ng/ml per year). Initial studies found that a velocity of > 0.75 ng/ml per year was 72 % sensitive 95 % specific in predicting prostatic carcinoma in a man with PSA values under 10 mg/ml (Roscigno, et al., 2004). PSADT was established in untreated patients with known prostate cancer who were followed expectantly by urologists from Stanford University (Schmid, McNeal, & Stamey, 1993). PSADT takes into account the exponential increase of serum PSA over time reflecting a relative change, and thus, is completely different from PSAV (Table 2). The original formula for calculation is:

$$PSADT = \frac{\log 2 \times t}{\log(finalPSA) - \log(initialPSA)} \quad \textbf{(Equation 1)}$$

where t is the time between the two PSA determinations. PSADT has two major advantages when compared to PSAV. First, it is independent of the baseline PSA value. In the example in Table 2, patient A is more likely to have prostate cancer than patient B based on his shorter PSADT. Note that PSAV is identical in both patients. Secondly, PSADT is also independent of the assay, provided the same assay is used in a given patient (Semjonow, et al., 2000). Comparison of serial PSA measurements in men from different study populations using different assays should therefore be made using PSADT and not PSAV.

Given the fact that in the general population the distribution of PSA levels is less than 4 ng/ml in about 90% of cases, many men do not require immediate biopsy but instead are being followed with serial PSA determinations. Thus, the majority of men will be judged by their PSA kinetics. Since the current data for PSAV and PSADT are not yet conclusive, the clinical usefulness of both dynamic concepts should be further evaluated in ongoing prospective trials such as the European Randomized

Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Project (PLCO).

Table 2: Example for the difference between the two dynamic concepts

	Patient A	**Patient B**
PSA increase within 1 year (ng/ml)	3,6 → 4,4	7,6 → 8,4
PSA velocity (ng/ml per year)	0,8	0,8
PSA doubling time (years)	3,5	6,9

1.5.8 Complex Approaches for Improving the Specificity of PSA

Complex approaches include multivariate regression analysis, neural networks, decision tree analysis and nomograms. Although they are reported to produce useful results, these models (or approaches) are still in evaluation phase and they are not used in daily clinical routine.

1.5.9 Artificial Neural Networks

One of the earlier Artificial Neural Network (ANN) studies designed using data of 1,787 men with a serum PSA concentration of more than 4.0 ng./ml. (approximately 40% of the men also had suspicious findings on DRE). The neural network predicted the biopsy result with 87% overall accuracy, and its output threshold could be adjusted to achieve the desired trade-off between sensitivity and specificity (Snow, Smith, & Catalona, 1994).

Babaian et al explored the potential role of a neural network-derived algorithm in enhancing the specificity of prostate cancer detection compared with the determination of prostate-specific antigen (PSA) and free PSA (fPSA) while maintaining a 90% detection rate. One hundred fifty-one men were enrolled in a

prospective protocol to evaluate the incidence of cancer in a population of men who participated in an early-detection program and whose PSA level was between 2.5 and 4.0 ng/ml. A new neural network algorithm was developed with PSA, creatinine kinase, prostatic acid phosphatase, fPSA, and age as input variables to produce a single-valued prostate cancer detection index (PCD-I). Cancer was histologically confirmed in 24.5% (37 of 151) of the men. At a sensitivity of 92%, the specificity for percent fPSA was 11%. The new algorithm (PCD-I) demonstrated an additional enhancement of specificity to 62% at 92% sensitivity. Clinically, the PCD-I would result in a savings of 49% (74 of 151) of all biopsies or 63.6% (71 of 114) of all unnecessary biopsies (Babaian, et al., 2000).

Finne et al designed ANN and LR models constructed on the basis of data on total PSA, the proportion of free PSA, DRE, and prostate volume from 656 consecutive men (aged 55 to 67 years) with total serum PSA concentrations of 4 to 10 ng/ml in the randomized population-based prostate cancer screening study in Finland. Of the 656 men, 23% had prostate cancer and 77% had either normal prostatic histology or a benign disease. At a 95% sensitivity level, 19% of the false-positive PSA results could be eliminated by using the proportion of free PSA versus 24% with the LR model and 33% with the ANN model ($P < 0.001$). At 80% to 99% sensitivity levels, the accuracy of the ANN and LR models was significantly higher than that of the proportion of free PSA. At 89% to 99% sensitivities, the accuracy of the ANN was higher than that of LR ($P </= 0.001$). At clinically relevant sensitivity levels, the ANN and LR models based on total PSA, the proportion of free PSA, DRE, and prostate volume could reduce the number of unnecessary biopsies significantly better than the proportion of free PSA alone in men with total PSA levels in the range 4 to 10 ng/ml (Finne, et al., 2000).

Stephan et al performed a multicentre study to evaluate the diagnostic value of a %fPSA-based ANN in men with tPSA concentrations between 2 and 20 ng/ml. They enrolled 1188 men and developed ANN with input data of tPSA, %fPSA, patient age, prostate volume, and DRE status to calculate the risk for the presence of prostate

cancer within different tPSA ranges (2-4, 4.1-10, 2-10, 10.1-20, and 2-20 ng/ml) at the 90% and 95% specificity or sensitivity cut-offs, depending on the tPSA concentration. ROC analysis and cut-off calculations were used to estimate the diagnostic improvement of the ANN compared with %fPSA alone. In the low tPSA range (2-4 ng/ml), the ANN detected 72% and 65% of cancers at specificities of 90% or 95%, respectively. At 4-10 ng/ml tPSA, the ANN detected 90% and 95% of cancers with specificities of 62% and 41%, respectively. Use of the ANN with 2-10 ng/ml tPSA enhanced the specificity of %fPSA by 20-22%, thus reducing the number of unnecessary biopsies (C. Stephan, et al., 2002).

Remzi at al developed an ANN to predict the presence of prostate cancer and to predict the outcome of repeat prostate biopsies. 820 men with a PSA level between 4 and 10 ng/ml was used. Variables in the database consisted of age, PSA, f/t PSA ratio, DRE findings, PSA velocity, and the transrectal ultrasound-guided variables of prostate volume, transition zone volume, PSAD, and PSA-TZ. The ANN used in the analysis was an advanced multilayer perceptron selected for accuracy by a genetic algorithm. The repeat biopsy prostate cancer detection rate was 10% (n = 83). At 95% sensitivity, the specificity for ANN was 68% compared with 54%, 33.5%, 21.4%, 14.7%, and 8.3% for multivariate logistic regression analysis, f/t PSA ratio, PSA-TZ, PSAD, and total PSA, respectively. The ANN reduced unnecessary repeat biopsies by 68% in the study. The area under curve (AUC) was 83% for the ANN versus 79%, 74.5%, 69.1%, 61.8%, and 60.5% for multivariate analysis, f/t PSA ratio, PSA-TZ, PSAD, and total PSA, respectively (Remzi, et al., 2003).

Matsui et al examined the efficacy of an artificial neural network analysis. Two hundred and twenty-eight patients with PSA of 2–10 ng/ml were enrolled in the study. Two ANN models were constructed: ANN1 with patient age, total PSA, free to total PSA ratio, prostate volume, transition zone volume, PSA density and PSA-TZ density as input variables, and ANN2 with presumed circle area ratio, DRE findings and chief complaint added as variables. The predictive accuracies of the ANN models were compared with conventional PSA and volume-related parameters

and a logistic regression (LR) model by ROC curve analysis. Of 228 patients, 58 (25.5%) were diagnosed with prostate cancer. While ANN2 had a slightly larger AUC than ANN1 (0.782 versus 0.793, P = 0.8477), the AUC of ANN2 was significantly greater than those of ln(PSA), PSAD, PSATZ and free to total PSA ratio (P = 0.0004, 0.0230, 0.0304, and 0.0037, respectively). The accuracy of ANN2 was significantly better than that of LR analysis at 90 and 95% sensitivity levels (p = 0.0051 and p<0.0001, respectively). At 95% sensitivity level, ANN2 reduced unnecessary biopsies by 40.0% with a negative predictive value of 95.7% (Matsui, et al., 2004).

Porter at al studied on data from 3814 men participating in the Tyrol screening project. Prospectively collected data from two independent sites in the United States were used to validate the model independently. The Tyrol data was split randomly into three cross-validation sets, and a feed-forward, back error-propagation ANN was alternately trained on a combination of two of these data sets and validated on the remaining data set. Similarly, three LR models were produced and validated using identical cross-validation data sets. The Tyrol model with the median ROC AUC was then validated against the Virginia Mason (n = 491) and Stanford University (n = 483) data sets. The ROC AUCs for the three cross-validations were 0.74, 0.76, and 0.75 for the ANN and 0.75, 0.76, and 0.75 for the LR models. The mean ROC AUC for both ANN and LR was 0.75 with a standard deviation of 0.009 for ANN and 0.006 for LR. The ROC AUCs for the Virginia Mason and Stanford University data were 0.74 (both ANN and LR) and 0.73 (ANN) and 0.72 (LR), respectively. This model, designed to predict the prostate biopsy outcome, performed accurately and consistently when validated with data from two independent referral centres in the United States, suggesting that it generalizes well and may be of clinical utility to a broad range of patients (Porter, et al., 2005).

The nature of ANN limits their practical applicability. These models are not amenable to a paper based, portable and clinically applicable format. ANN requires computer support since complex calculations are necessary. Therefore, they cannot

be distributed to a wide array of clinical users in a format similar to prostate cancer nomograms (Karakiewicz, et al., 2005).

1.5.10 Regression Analysis and Nomograms

Another approach to predict prostatic carcinoma is to prepare nomograms (Figure 3).

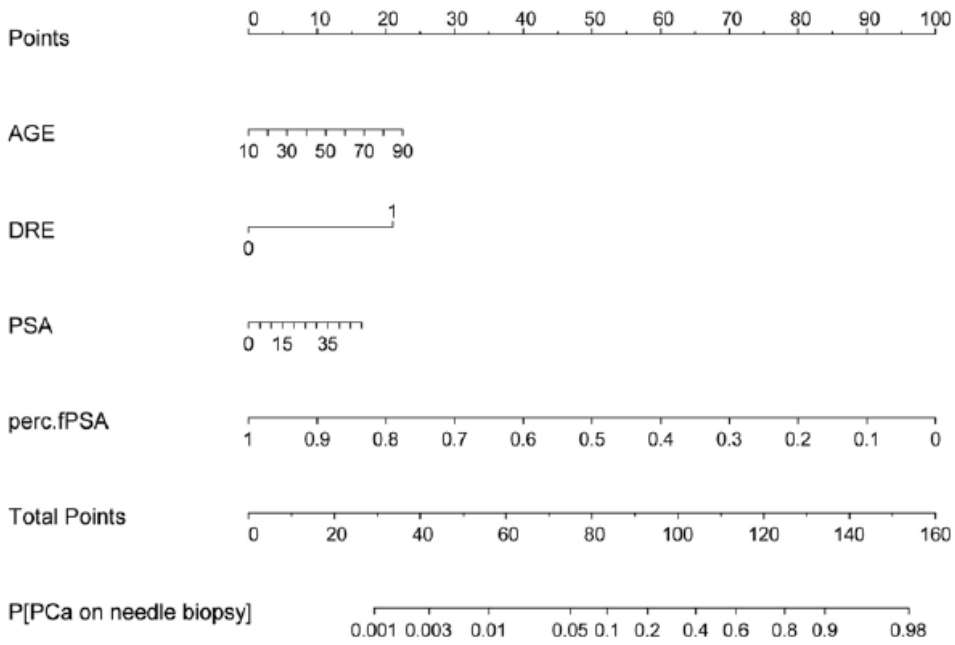

Figure 3: Nomogram predicting probability of prostate cancer on needle biopsy using age, DRE, serum PSA and %fPSA. DRE 0, benign. DRE 1, suspicious for cancer. perc.fPSA, %fPSA. P[PCa on needle biopsy], probability of prostate cancer on needle biopsy (Karakiewicz, et al., 2005).

A nomogram or nomograph is a graphical calculating device, a two-dimensional diagram designed to allow the approximate graphical computation of a function. It can be based on any type of function, such as logistic regression or Cox regression models.

The nomogram usually incorporates continuous or categorical variables. The effect of the variables on the outcome of interest is represented in the format of axes and risk points are attributed according to the prognostic/predictive importance of the variable of interest. The nomogram format is unique because it allows combining the input of several continuously coded variables or that of several categorically coded variables. This format distinguishes nomograms from look-up tables or decision trees, where continuously coded variables cannot be processed (Shariat, Margulis, Lotan, Montorsi, & Karakiewicz, 2008). Binary logistic regression based nomograms were reported to be the most useful (Chun, et al., 2007; Kawakami, et al., 2008).

Several studies on nomograms are summarized in Table 3.

Table 3: Predictive accuracy of various prostate cancer nomograms

References	Prediction of prostate cancer on needle biopsy	AUC
(Eastham, May, Robertson, Sartor, & Kattan, 1999)	Age, race, DRE, PSA (0–4 ng/ml)	0.75
(Garzotto, et al., 2003)	Age, race, family history, referral indications, prior vasectomy, DRE, PSA (10 ng/ml or less), TRUS findings	0.73
(Lopez-Corona, et al., 2003)	Age, family history, PSA, PSA slope, DRE, data from initial biopsy, cumulative	0.70
(Karakiewicz, et al., 2005)	Age, PSA, DRE	0.69
(Karakiewicz, et al., 2005)	Age, PSA, %fPSA, DRE	0.77

1.5.11 Decision Tree Classification (Recursive Partitioning)

There are several algorithms for building decision trees (DT). The algorithm builds a decision tree structure and classifies subjects into several risk levels. It can be used simply to explore the data, identify possible high-risk subgroups, and uncover

interactions or effect modifications among prognostic factors. The most widely known is Classification and Regression Tree (CRT, also known as CART). Another one which is used in this study is Quick, Unbiased and Efficient Statistical Tree (QUEST) which was developed by Loh and Shih (Loh & Shih, 1997).

There are four studies in the literature using decision tree classification on prostate cancer prediction problem. Details of these studies are presented below.

Garzotto et al, performed a study to identify risk factors and risk groups for carcinoma detection in men undergoing repeat prostate biopsies. Risk factors for a subsequent diagnosis of prostate carcinoma were identified using the log-rank test and a stepwise, stratified Cox regression model. Based on the risk factors identified by Cox regression analysis, recursive partitioning was further used for risk stratification. Recursive partitioning identified four distinct risk groups that were characterized by their PSADT and PSAD and the presence of high grade PIN and had estimated 2-year and 5-year carcinoma detection rates of 3±1% and 21±4%, 28±5% and 40±7%, 22±6% and 58±8%, and 66±9% and 100%, respectively (Garzotto, Park, et al., 2005).

In another study of Garzotto et al, they tried to build a decision tree for patients suspected of having prostate cancer using CART analysis. Data were collected on 1,433 referred men with a serum PSA levels of < or = 10 ng/mL who underwent a prostate biopsy. Factors analyzed included demographic, laboratory, and ultrasound data (ie, hypoechoic lesions and PSA density). CART analysis was performed in two steps, initially using PSA and DRE alone and subsequently using the remaining variables. CART analysis selected a PSA cut-off of more than 1.55 ng/mL for further work-up, regardless of DRE findings. CART then selected the following subgroups at risk for a positive biopsy: (1) PSAD more than 0.165 ng/mL/cc; (2) PSAD < or = 0.165 ng/mL/cc and a hypoechoic lesion; (3) PSAD < or = 0.165 ng/mL/cc, no hypoechoic lesions, age older than 55.5 years, and prostate volume < or = 44.0 cc; and (4) PSAD < or = 0.165 ng/mL/cc, no hypoechoic lesions, age older than 55.5 years, and 50.25 cc less than prostate volume < or = 80.8 cc. In the validation data

set, specificity and sensitivity were 31.3% and 96.6%, respectively. Cancers that were missed by the CART were Gleason score 6 or less in 93.4% of cases. ROC AUC analysis showed that CART and LR models had similar accuracy (AUC = 0.74 v 0.72, respectively) (Garzotto, Beer, et al., 2005).

Nam et al evaluated examined a cohort of 2,637 men who underwent prostate biopsies for abnormal DRE or PSA. Using risk factors for prostate cancer, including patient age, ethnicity, family history of prostate cancer, previous negative biopsy, voiding symptoms and prostate volume, they developed risk groups for prostate cancer using recursive partitioning modelling independent of PSA or DRE. Of the 2,637 men 1,282 (48.6%) had prostate cancer. Age, ethnicity, family history, previous negative biopsy and prostate volume were predictive for cancer. They constructed 6 risk groups by combining these factors and created tables to assign patients to these groups. Independent of PSA and DRE the probability of cancer ranged from 15% in patients in group 1 to 78% in patients in group 6 ($p < 0.0001$). By adding PSA and DRE to each risk group prostate cancer probabilities were refined from 0% to 100%. Patients in the higher risk groups also had higher grade cancer ($p < 0.0001$) (Nam, et al., 2006).

Spurgeon et al collected data on 1,563 consecutive referred men with serum PSA 10 ng/ml or less who underwent an initial prostate biopsy. Predictors of aggressive cancer (Gleason sum 7 or greater) were identified using CART analysis. Cancer was detected in 406 men (26.1%). Gleason 7 or greater cancer was found in 130 men (8.3%). CART created a decision tree that identified certain groups at risk for aggressive cancer, namely 1) PSAD greater than 0.165 ng/ml/cc, and 2) PSAD greater than 0.058 to 0.165 ng/ml/cc or less, age greater than 57.5 years and prostate volume greater than 22.7 cc. The incidence of aggressive prostate cancer was 1.1% when PSAD was 0.058 ng/ml/cc or less in the validation set. The sensitivity and specificity of CART for identifying men with aggressive cancer were 100% and 31.8% for model building data, and 91.5% and 33.5% for the validation data set, respectively. Application of this CART could decrease unnecessary biopsies by

33.5% when only a diagnosis of high grade prostate cancer would lead to subsequent therapy (Spurgeon, et al., 2006).

Several studies have assessed also pre-treatment prognostic factor in men with prostatic carcinoma using decision tree classification (Banerjee, Biswas, Sakr, & Wood, 2000; Gretzer, Epstein, Pound, Walsh, & Partin, 2002; Shipley, et al., 1999; Williams, et al., 2004).

1.5.12 Genetic Algorithm

To our knowledge, no genetic algorithm study on prostate biopsy decision is present in the medical literature. Genetic algorithm is a relatively new data mining technique which is a good candidate for investigating problems that are not well understood, and they are useful when there are too many combinations to search from. GA can provide quick solutions to combinatorial optimisation problems; not necessarily the best solution, but often one of the good solutions. This drawback can be overcome by running consecutive tests with different GA parameters such as modifying the population size, mutation and crossover rate, and using the best results. There are advantages of using GA in medical data mining tasks. Firstly, GA results can be expressed in natural language as simple rules. Secondly, GA can select subsets of variables from a pool of variables without being specified to do so (Goldberg, 1989).

1.6. Biopsy

If abnormalities are detected on the DRE or PSA test, patients should undergo urologic evaluation with transrectal ultrasound-guided prostate biopsy. No further urologic evaluation is necessary in patients who have an unremarkable DRE and a normal serum PSA level, because the incidence of prostate cancer is only 0.4 percent in this group.

Transrectal ultrasound examination and guided prostate biopsies are office-based procedures that are well tolerated by patients. The procedures require no adjuvant sedation or analgesia. Rare complications of transrectal prostate biopsy include rectal bleeding and sepsis. Most patients report only mild rectal spotting, hematospermia or hematuria after the test (Naitoh, et al., 1998).

1.7. Incidence of Prostatic Carcinoma

Estimated incidence is 161 per 100000 male in USA (Jemal, et al.). However, prostatic carcinoma is an indolent disease which can be silent for years. It is a cancer all men will get if they live long enough (Stamey, 2004). An autopsy study in men also serves to emphasize the critical relationship of prostate cancer with age; 2% of men in their twenties had prostate cancer, rising steadily and linearly with each decade until 64% had prostate cancer in their sixties (Sakr, et al., 1994).

Most of the cases are not known, and they usually die because of other causes after decades. Some authors suspects of overtreatment for prostate cancer caused by the use of PSA levels in the USA (Stamey, 2004).

In an epidemiologic study performed in Izmir, the incidence of prostate cancer was 4.2 per 100000 male, and similar to that observed in other Asian populations. The incidence of prostate cancer varies widely between countries and ethnic groups, and differences in genes associated with androgen metabolism or inherited susceptibility may explain some of this variability. The incidence in Turkish men who have migrated to Australia was six times higher suggesting that underdiagnosis accounts for the low recorded rates, which are readily inflated by examination of prostatic tissue obtained during trans-urethral prostatectomies, or by PSA screening (Fidaner, Eser, & Parkin, 2001). Another cause of this drastic difference in rates may be overdiagnosis in USA.

Generally, PSA between 4-10 ng/ml is accepted as having 70 % sensitivity and 70 % specificity (Roscigno, et al., 2004). The value of predictive tests closely related to

prevalence of the disease. Naturally, the prevalence of prostatic carcinoma may change according to geographical place and time.

Positive predictive value (PPV) is one of the tests that are affected by prevalence as seen in Equation 2 (Ingelfinger, 1983).

$$PPV = \frac{Sensitivity \times \Pr obability}{Sensitivity \times \Pr obability + (1 - Specifity)(1 - \Pr obability)} \quad \textbf{(Equation 2)}$$

In medical literature, there are a few studies related to PPV of PSA (Arai, et al., 1997; Hernandez & Thompson, 2004). However, when the articles was examined, it is seen that the authors have a problem of terminology, in fact they calculated likelihood ratio of a positive result which is sensitivity/(1 – specificity) (Ingelfinger, 1983).

Positive predictive value can be also calculated as True Positive/(True Positive+False Positive). Conversely, Negative Predictive Value (NPV) is True Negative/(True Negative+False Negative) (Ingelfinger, 1983).

Effect of prevalence on clinical value of the test can be demonstrated. If the prevalence is 10% (Table 4); unnecessary biopsies are 79%, cost of one case of early detection is 4.9 biopsies, and missed cases are 3%.

Table 4: Result of the test on 1000 cases if the prevalence is 10%.

		Carcinoma		**Total**
		+	**-**	
Test	**+**	70	270	340
	-	30	630	660
Total		100	900	1000

On the other hand, if the prevalence is 1% (Table 5); unnecessary biopsies are 98%, cost of one case of early detection is 43.4 biopsies, and missed cases are 0.3%.

Table 5: Result of the test on 1000 cases if the prevalence is 1%.

		Carcinoma		Total
		+	-	
Test	+	7	297	304
	-	3	693	696
Total		10	990	1000

1.8. Clinical Decision Support Systems

Computerized clinical decision support systems (CDSSs) are information systems designed to improve clinical decision making. The CDSS improved practitioner performance in the majority of the applications (Garg, et al., 2005).

Three decades after the introduction of computerized decision support (Shortliffe, Axline, Buchanan, Merigan, & Cohen, 1973), it is still far from being widely used. Sometimes the basis for a decision support system is clinical guidelines, which unfortunately are also still not widely used in daily clinical practice. According to a systematic review (Cabana, et al., 1999), potential barriers to physicians' guideline adherence are lack of awareness, lack of familiarity, lack of agreement, lack of self-efficacy, lack of outcome expectancy, the inertia of previous practice, and external barriers.

Among the sources of medical information, CDSS is one of the most reliable and less time consuming (Hayward, El-Hajj, Voth, & Deis, 2006). However, in the USA only 40.8% of the physicians use CDSS (Grant, Campbell, Gruen, Ferris, & Blumenthal, 2006). Some studies have been performed to evaluate the physician's approach to

CDSS. According to another study (Sittig, Krall, Dykstra, Russell, & Chin, 2006), adult primary care physicians stated that the CDSS provided "helps them take better care of their patients" (3.6 on scale of 1:Never, 5:Always), "is worth the time it takes" (3.5), and "reminds them of something they've forgotten" (3.2). Interestingly, 80% said they were less likely to accept alerts when they were behind schedule and 84% of clinicians admitted to being at least 20 minutes behind schedule "some", "most", or "all of the time". They state that "Even though a majority of our clinical decision support suggestions are not explicitly followed, clinicians feel they are of benefit and would be even more beneficial if they had more time available to address them". In another study on assessment and management of cardiovascular risk, the physicians reported that the most significant drawback was the extra time needed in consultation (Wilson, Duszynski, Turnbull, & Beilby, 2007). Some of the important barriers which have been found in an interview study of general practitioners (GPs) were; limited computer skills, shortage of time during consultation, problems with interpreting the recommendations given, and the GPs' concerns about patient reactions (Short, Frischer, & Bashford, 2004). In another study on an automated feedback system which generates real-time comments on the appropriateness of diagnostic tests ordered by GPs, the most frequently mentioned reason to reject the recommendation was disagreement with the content and/or the recommendations in the practice guidelines (Bindels, Hasman, Derickx, Van Wersch, & Winkens, 2003).

For prediction of prostate cancer, some decision support tools called "calculators" on the web are also available (Parekh, et al., 2006).

1.9 Aim of the Study

As seen in above literature review, PSA is the most important marker for tumour screening, but suffers from weak sensitivity and specificity. Several approaches have been developed to obtain a better sensitivity and specificity up to date. None of these approaches widely accepted, and they usually designed at satisfy needs in certain

circumstances. Real incidence of prostate cancer is very high, but most of the men die of other causes without knowledge of their disease. Slow nature of disease complicates the problem; because some true positives can be accepted as negative cases (it is better not to know the presence of the disease).

Studies on prostate cancer prediction problem have been mostly performed Western populations; however incidence of the disease is lower in Turkey. The same prediction models would not have work for Turkish population. So we need to study the problem on the Turkish population to see if different approaches are possible for Turkish population.

The aim of this study was to produce a model to predict correct timing of prostate biopsy for Turkish population. The model was produced by testing all known parameters with several methods to provide a best approach to the problem. The established model was used in a decision support system which will support the physician in biopsy decision. The approach of the physicians to the decision support system has been also evaluated.

CHAPTER 2

METHODS

2.1 Patients

All the TRUS guided prostatic biopsy cases who admitted to Akdeniz University Hospital Urology Department in period of January 2000- April 2007 evaluated retrospectively. TRUS guided biopsy can be performed only in Akdeniz University in Antalya district. Antalya district has a population of 1 789295 (TUİK, 2007). A total of 1878 biopsies were performed during the period. We included 1453 initial biopsy patients who have serum PSA level, age, DRE, and biopsy results available to the study.

2.2 Data

Akdeniz University Hospital Information System (HIS) and paper based biopsy records of Urology Department will be used as data sources. HIS contains the demographic information about all patients, PSA, fPSA, cPSA, and other laboratory data of last eight years, and pathology reports of the patients. Biopsy records contain DRE results of the patients. Gleason grades of the tumours were available from pathology reports. Gleason grades 7-10 considered as high grade malignancy (poor

prognosis) (Humphrey, 2004) and additional analyses were performed for estimation of patients with poor prognosis. The prostate volume were calculated by the ellipsoid formula (length (cm) * width (cm) * height (cm) * (p/6)) (Kälkner, et al., 2006).

2.3 Analysis

SPSS 15.0 (Statistical Package for Social Sciences, SPSS Inc, Chicago, Illinois, USA) was used for statistical analysis including decision trees. Some specifications and additional software are listed below;

Logistic regression analysis; Forward conditional stepwise analysis with 0.5 entry and 0.10 removal criteria was performed. Hosmer-Lemeshow goodness of fit test was also performed for each model. Forward and backward conditional stepwise methods were applied because of multicollinearity of the variables. Forward method was selected because of better performance in Hosmer-Lemeshow goodness of fit test.

Decision trees In the analysis, dependent variable was diagnosis which is composed of two classes namely, benign and malign. Independent variables were age (numeric), PSA (numeric), free PSA (numeric), percent free PSA (numeric), DRE I (DRE I, class I: negative, class II: suspicious, class III: positive), DRE II (class I: negative, class II: suspicious or positive). Decision tree algorithms in SPSS were used for decision tree classification. CRT technique was selected for its performance was superior to other algorithms. Additionally, analysis by QUEST algorithm was performed by QUEST Classification Tree (version 1.9.2, http://www.stat.wisc.edu/~loh/quest.html).

Artificial neural networks: The ANN program SimMine (SimWorld Limited, London, UK, www.simworld.co.uk) used in this study. The system uses back-propagation method.

Genetic algorithms: The GA program SimMine (SimWorld Limited, London, UK, www.simworld.co.uk) used in this study. The system allows the selection of flat or

hierarchical chromosome types, allows preprocessing the data by scaling, taking first differences, and dividing continuous data into categories. As the input parameters are a mixture of numerical and coded values, the system converts numerical values into a number of categories. Users can select 2, 3, 4 or 5 categories and the system automatically classifies data by grouping them into an equal number of samples in each category. There are alternative ways of dividing data into categories, and the method employed here is in line with the statistical requirements of distributions. The data mining system allows users to select the total number of chromosomes (the population size) and the number of top-scoring individuals that survive to the next generation. When the GA puts forward a hypothesis, the system counts the number of samples covered by this hypothesis. The standard fitness score for the GA is expressed by a simple fitness function: Fitness score = (true_positive/positive_count) – (false_positive/negative_count)

As can be seen above, the GA would achieve a maximum score of 1 if it identified all the positive's correctly and had a false_positive of 0. In the GA analysis we used the default population size of 128, and the top-scoring 32 individuals were selected to continue into the next generation of solutions. The search was stopped after no improvement was seen for the last 25 iterations of each run. The default value for the crossover rate was 60% and for the mutation rate 20% per chromosome. In most cases, the system quickly converged to a solution, given the small size of the data set. Numerical values were automatically converted into a 2-coded system.

Test groups: For ANN, LR, DT and GA, the group was divided into study and test groups. Twenty-five percent (363 of 1453 cases) is randomly selected as test group.

2.4. Web Site

Development of decision support tool: Microsoft .Net Framework version 2.0 (Microsoft Visual Studio 2005, Microsoft Visual C# 2005) is used to develop the web based application. A hybrid algorithm was prepared which gives the probability

of malignancy and probability of high grade malignancy. After age, serum PSA level, serum free PSA level (optional), and DRE results are entered, the system gives the possibilities of malignancy and high grade malignancy. The system produces the result as “The probability of malignancy is high” when the probability of malignancy exceeds 50%, “The probability of high grade malignancy is high” when the probability of high grade malignancy exceeds 20%, and “The probability of malignancy is very low” when the probability is under 1%. The system was published on a website (http://www.prostatca.org). A user questionnaire has also been implemented on the website.

User questionnaire: The questionnaire was composed of 24 questions including 15 Likert type questions and one open-ended question to collect opinions and suggestions from users. The website was announced on two discussion groups on the Internet, and an article about the website has been published in a national medical magazine. After four months of data collection, the answers to the questionnaires have been evaluated.

CHAPTER 3

RESULTS

3.1. Analysis of the Whole Group

From the files of urology, records of 1878 patients who had TRUS guided prostate biopsy in 6.5 years period had been obtained. After recurrent biopsies had been excluded, 1453 patients who have sufficient data (age, serum PSA level, DRE, biopsy diagnosis) included in the study (Table 6).

Table 6: General characteristics of the cases.

Variable	n	Mean	Standard Deviation	Median	Minimum	Maximum
Age	1453	64.4	8.5	64	38	92
PSA	1453	16.9	64.1	7.7	0.05	1500
fPSA	1039	3.0	12.2	1.2	0.03	216
fPSA/PSA	1039	21.6	13.6	18.07	1	100
Volume	1368	35.1	19.1	30.6	0.1	151.5
PSAD	1368	0.65	4.28	0.22	0.01	143.07

3.1.1. Overall PSA Results

The patients are classified according to prebiopsy serum PSA level. The results are shown in Table 7. The results of normal DRE and abnormal DRE patients are shown in Table 8 and Table 9.

Table 7: Percent of malignant and benign biopsy results according to prebiopsy PSA level.

PSA	Benign		Adenocarcinoma		Total	
	n	%	n	%	n	%
0-2,5	146	85.4	25	14.6	171	100.0
2,51-4	85	88.5	11	11.5	96	100.0
4,01-6	208	85.6	35	14.4	243	100.0
6,01-10	365	74.9	122	25.1	487	100.0
Over 10	222	48.7	234	51.3	456	100.0
Total	1026	70.6	427	29.4	1453	100.0

Table 8: Percent of malignant and benign biopsy results according to prebiopsy PSA level in men with a normal DRE

PSA	Benign		Adenocarcinoma		Total	
	n	%	n	%	n	%
0-2.5	24	88.9	3	11.1	27	100.0
2.51-4	17	89.5	2	10.5	19	100.0
4.01-6	125	91.9	11	8.1	136	100.0
6.01-10	245	83.3	49	16.7	294	100.0
Over 10	118	65.9	61	34.1	179	100.0
Total	529	80.8	126	19.2	655	100.0

Table 9: Percent of malignant and benign biopsy results according to prebiopsy PSA level in men with an abnormal DRE.

PSA	Benign		Adenocarcinoma		Total	
	n	%	n	%	n	%
0-2.5	122	84.7	22 (%)	15.3	144	100.0
2.51-4	68	88.3	9 (%)	11.7	77	100.0
4.01-6	83	77.6	24 (%)	22.4	107	100.0
6.01-10	120	62.2	73 (%)	37.8	193	100.0
Over 10	104	37.5	173 (%)	62.5	277	100.0
Total	497	62.3	301 (%)	37.7	798	100.0

Sensitivity and specificity levels for various PSA cut-off values are shown in table 10.

Table 10: Sensitivity and specificity levels for various PSA cut-off values.

PSA cut-off value	Overall		Normal DRE		Abnormal DRE	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
2.5	0.94	0.14	0.98	0.05	0.93	0.25
4	0.92	0.23	0.96	0.08	0.90	0.38
6	0.83	0.43	0.87	0.31	0.82	0.55
10	0.55	0.78	0.48	0.78	0.57	0.79

Positive predictive value of PSA according to various cut-off values has shown in Table 11.

Table 11: Positive predictive value (PPV) and negative predictive value (NPV) levels for various PSA cut-off values.

PSA cut-off value	**Overall**		**Normal DRE**		**Abnormal DRE**	
	PPV	NPV	PPV	NPV	PPV	NPV
2.5	0.31	0.85	0.20	0.89	0.43	0.85
4	0.33	0.87	0.20	0.89	0.47	0.86
6	0.34	0.86	0.23	0.91	0.52	0.83
10	0.50	0.81	0.34	0.86	0.62	0.75

PSA levels show correlation with age ($r=0.234$, $p<0.001$) and prostate volume ($r=0.293$, $p<0.001$). In patients who have negative biopsy results, PSA level also show correlation with age ($r=0.155$, $p<0.001$) and prostate volume ($r=0.442$, $p<0.001$).

3.1.2. PSA Density

Prostate volume data is available for 1368 patients. PSA densities in malignant and benign patients are shown in Table 12.

Table 12: PSA density of malignant and benign patient groups.

Group	n	Median	Interquartile range	p
Benign	974	0.19	0.17	<0.001
Malignant	394	0.39	0.69	
Total	1368	0.22	0.25	

When we take cut-off value of 0.25 to detect 70 % of malignant cases (sensitivity is 0.70), specificity is 0.68 (Table 13).

Table 13: Distribution of cases when PSA density cut-off value is taken as 0.25 (p<0.001).

		PSA density				Total	
		< 0.25		>=0.25			
		n	%	n	%	n	%
Diagnosis	**Benign**	658	67.6	316	32.4	974	100
	Malignant	117	29.7	277	70.3	394	100
Total		775	56.7	593	43.3	1368	100

PSA density cut-off values for 0.90, 0.80, and 0.70 sensitivity levels are shown in Table 14.

Table 14: PSA density cut-off values for 0.90, 0.80, and 0.70 sensitivity levels.

PSA density cut-off level	Sensitivity	Specificity
0.13	0.90	0.28
0.18	0.80	0.46
0.25	0.70	0.68

Comparison of ROC AUC's for PSA and PSA density is shown in Figure 4. ROC AUC statistics of PSA density compared to PSA for malignancy are shown in Table 15.

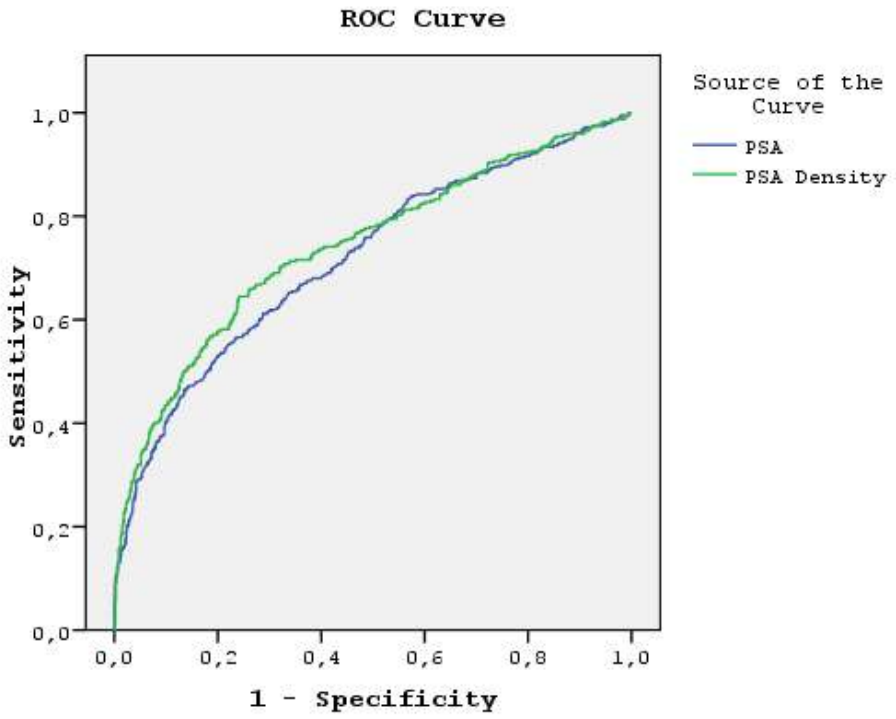

Figure 4: Comparison of ROC AUC's for PSA and PSA density

Table 15: ROC AUC parameters of PSA and PSA density.

Variable	n	AUC	95% CI	p
PSA	1453	0.720	0.690-0.750	0.000
PSA density	1368	0.740	0.709-0.771	0.000

3.1.3. Age Specific Analysis

The patients divided into groups of 10 years (decades). Fifth decade is 40-49, 6th decade is 50-59, 7th decade is 60-69, and 8th decade is 70-79 years old patients. Sensitivity and specificity values for different PSA cut-off values for each decade are shown in Table 16, Table 17, Table 18 and Table 19. Ninety percent sensitivity level is shown as bold in the tables.

Table 16: Sensitivity and specificity levels for various PSA cut-off values in 5th decade patients (Ca: cancer).

PSA	Under		Over		Total		Sensitivity	Specificity
	Ca/total	%	Ca/total	%	Ca/total	%		
2.5	1/14	7.1	8/32	25.0	9/46	19.6	0.89	0.35
4	1/18	5.6	8/28	28.6	9/46	19.6	0.89	0.46
5	1/21	4.8	8/25	32.0	9/46	19.6	0.89	0.54
6	2/27	7.4	7/19	36.8	9/46	19.6	0.78	0.68
7	3/30	10.0	6/16	37.5	9/46	19.6	0.67	0.73
8	4/33	12.1	5/13	38.5	9/46	19.6	0.56	0.78
9	4/36	11.1	5/10	50.0	9/46	19.6	0.56	0.86
10	4/38	10.5	5/8	62.5	9/46	19.6	0.56	0.92

Table 17: Sensitivity and specificity levels for various PSA cut-off values in 6th decade patients (Ca: cancer).

PSA	Under		Over		Total		Sensitivity	Specificity
	Ca/total	%	Ca/total	%	Ca/total	%		
2.5	8/55	14.5	63/328	19.2	71/383	18.5	0.89	0.15
4	10/85	11.8	61/298	20.5	71/383	18.5	0.86	0.24
5	17/125	13.6	54/258	20.9	71/383	18.5	0.76	0.31
6	20/177	11.3	51/206	24.8	71/383	18.5	0.72	0.50
7	26/218	11.9	45/165	27.3	71/383	18.5	0.63	0.62
8	31/250	12.4	40/133	30.1	71/383	18.5	0.56	0.70
9	37/274	13.5	34/109	31.2	71/383	18.5	0.48	0.76
10	41/297	13.8	30/86	34.9	71/383	18.5	0.42	0.82

Table 18: Sensitivity and specificity levels for various PSA cut-off values in 7th decade patients (Ca: cancer).

PSA	Under		Over		Total		Sensitivity	Specificity
	Ca/total	%	Ca/total	%	Ca/total	%		
2.5	8/58	13.8	148/519	28.5	156/577	27.0	0.95	0.12
4	16/101	15.8	140/476	29.4	156/577	27.0	0.90	0.20
5	22/140	15.7	134/437	30.7	156/577	27.0	0.86	0.28
6	32/194	16.5	124/383	32.4	156/577	27.0	0.79	0.38
7	54/270	20.0	102/307	33.2	156/577	27.0	0.65	0.51
8	63/326	19.3	93/251	37.1	156/577	27.0	0.60	0.62
9	73/374	19.5	83/203	40.9	156/577	27.0	0.53	0.71
10	78/411	19.0	78/166	47.0	156/577	27.0	0.50	0.79

Table 19: Sensitivity and specificity levels for various PSA cut-off values in 8th decade patients (Ca: cancer).

PSA	Under		Over		Total		Sensitivity	Specificity
	Ca/total	%	Ca/total	%	Ca/total	%		
2.5	8/43	18.6	180/395	45.6	188/438	42.9	0.96	0.14
4	9/62	14.5	179/376	47.6	188/438	42.9	0.95	0.21
5	12/82	14.6	176/356	49.4	188/438	42.9	0.94	0.28
6	17/111	15.3	171/327	52.3	188/438	42.9	0.91	0.38
7	31/150	20.7	157/288	54.5	188/438	42.9	0.84	0.48
8	43/183	23.5	145/255	56.9	188/438	42.9	0.77	0.56
9	52/211	24.6	136/227	59.9	188/438	42.9	0.72	0.64
10	69/245	28.2	119/193	61.7	188/438	42.9	0.63	0.70

Comparison of ROC AUCs are shown in Table 20. Sensitivity and specificity values of DRE negative patients for different PSA cut-off values for each decade are shown in Table 21, Table 22, Table 23 and Table 24.

Table 20: PSA ROC AUCs according to decades. CI: Confidence interval.

Decade	n	AUC	95% CI	p
5^{th}	45	0.814	0.651-0.977	0.004
6^{th}	393	0.663	0.588-0.738	0.000
7^{th}	577	0.668	0.615-0.720	0.000
8^{th}	438	0.753	0.707-0.799	0.000
Overall	1453	0.720	0.690-0.750	0.000

Table 21: Sensitivity and specificity levels for various PSA cut-off values in 5th decade DRE negative patients (Ca: cancer).

PSA	Under		Over		Total		Sensitivity	Specificity
	Ca/total	%	Ca/total	%	Ca/total	%		
2.5	0/2 (0.0)	0.0	5/20	25.0	5/22	22.7	1.00	0.12
4	0/2 (0.0%)	0.0	5/20	25.0	5/22	22.7	1.00	0.12
5	0/5 (0.0%)	0.0	5/17	29.4	5/22	22.7	1.00	0.29
6	1/10 (%)	10.0	4/12	33.3	5/22	22.7	0.80	0.53
7	1/11 (%)	9.1	4/11	36.4	5/22	22.7	0.80	0.59
8	2/14 (%)	14.3	3/8	37.5	5/22	22.7	0.60	0.71
9	2/16 (%)	12.5	3/6	50.0	5/22	22.7	0.60	0.82
10	2/17 (%)	11.8	3/5	60.0	5/22	22.7	0.60	0.88

Table 22: Sensitivity and specificity levels for various PSA cut-off values in 6th decade DRE negative patients (Ca: cancer).

PSA	Under		Over		Total		Sensitivity	Specificity
	Ca/total	%	Ca/total	%	Ca/total	%		
2.5	1/11	9.1	25/192	13.0	26/203	12.8	0.96	0.06
4	2/19	10.5	24/184	13.0	26/203	12.8	0.92	0.10
5	5/47	10.6	21/156	13.5	26/203	12.8	0.81	0.24
6	6/77	7.8	20/126	15.9	26/203	12.8	0.77	0.39
7	10/103	9.7	16/100	16.0	26/203	12.8	0.62	0.53
8	13/130	10.0	13/73	17.8	26/203	12.8	0.50	0.66
9	16/146	11.0	10/57	17.5	26/203	12.8	0.38	0.73
10	17/161	10.6	9/42	21.4	26/203	12.8	0.35	0.81

Table 23: Sensitivity and specificity levels for various PSA cut-off values in 7th decade DRE negative patients (Ca: cancer).

PSA	Under		Over		Total		Sensitivity	Specificity
	Ca/total	%	Ca/total	%	Ca/total	%		
2.5	1/10	10.0	48/276	17.4	49/286	17.1	0.98	0.04
4	2/18	11.1	47/268	17.5	49/286	17.1	0.96	0.07
5	3/35	8.6	46/251	18.3	49/286	17.1	0.94	0.14
6	7/72	9.7	42/214	19.6	49/286	17.1	0.86	0.27
7	18/124	14.5	31/162	19.1	49/286	17.1	0.63	0.45
8	22/161	13.7	27/125	21.6	49/286	17.1	0.55	0.59
9	24/188	12.8	25/98	25.5	49/286	17.1	0.51	0.69
10	29/218	13.3	20/68	29.4	49/286	17.1	0.41	0.80

Table 24: Sensitivity and specificity levels for various PSA cut-off values in 8th decade DRE negative patients (Ca: cancer).

PSA	Under		Over		Total		Sensitivity	Specificity
	Ca/total	%	Ca/total	%	Ca/total	%		
2.5	1/3	33.3	45/139	32.4	46/142	32.4	0.98	0.02
4	1/6	16.7	45/136	33.1	46/142	32.4	0.98	0.05
5	2/12	16.7	44/130	33.8	46/142	32.4	0.96	0.10
6	2/22	9.1	44/120	36.7	46/142	32.4	0.96	0.21
7	7/39	17.9	39/103	37.9	46/142	32.4	0.85	0.33
8	11/54	20.4	35/88	39.8	46/142	32.4	0.76	0.45
9	13/66	19.7	33/76	43.4	46/142	32.4	0.72	0.55
10	17/78	21.8	29/64	45.3	46/142	32.4	0.63	0.64

Prebiopsy PSA ROC AUCs according to decades for DRE negative patients are shown in Table 25.

Table 25: PSA ROC AUCs according to decades for DRE negative patients

Decade	**n**	**AUC**	**CI**	**p**
5th	22	0.788	0.532-1.000	0.055
6th	203	0.607	0.490-0.724	0.078
7th	286	0.622	0.530-0.717	0.007
8th	142	0.702	0.607-0.797	0.000
Overall	655	0.669	0.613-0.724	0.000

According to decades, 90% sensitivity levels for serum PSA level are shown in Table 26.

Table 26: Serum PSA cut-off levels for 90% sensitivity.

Decade	PSA cut-off level	
	All patients	DRE(-) patients
5	2.5	5
6	2.5	4
7	4	5
8	6	6
Total	4	5

3.1.4. Ratio of free/total PSA (PSA Percent)

Free PSA serum level is available in 1038 patients. Distribution of the cases according to 25 % fPSA/PSA cut-off is shown in Table 27. Sensitivity for malignancy is 0.77 for this level. Free PSA and Free/total PSA percent ROC AUC's are shown in table 28.

Table 27: Distribution of the patients according to a cut-off of 25 % or less free PSA/PSA.

25% or less		**>25%**		p
Carcinoma/total	%	Carcinoma/total	%	
213/744	28.6	62/294	21.1	0.013

Table 28: Free PSA and Free/total PSA ROC AUC.

Variable	**n**	**AUC**	**95% CI**	**p**
Free PSA	1038	0.655	0.616-0.694	0.000
Free/total PSA	1038	0.599	0.559-0.639	0.000

3.1.5. Summary by ROC AUCs of Classical Approaches

The highest AUC is seen in PSA of 5th decade. However, the number of patients in this group is very low (n=45). AUC of PSA in 8th decade is also high. PSA density AUC is also higher than PSA serum level AUC (Table 29).

Table 29: Summary of ROC AUCs of classical approaches.

Variable	ROC AUC
PSA	0.720*
5^{th} decade	0.814*
6^{th} decade	0.663*
7^{th} decade	0.668*
8^{th} decade	0.753*
Free PSA	0.655*
PSA percent	0.599*
PSA density	0.740*

* indicates statistical significance from ROC AUC of 0.5.

3.1.6. Dynamic Concepts

In our patient group, previous PSA measures were available for 283 benign cases and 63 malignant cases. PSA velocity was median 0.43/year for benign cases and 0.68/year for malignant cases (p=0.326). PSA doubling time was median 2.2 years for benign cases and 1.9 years for malignant cases (p=0.961).

3.1.7 Logistic Regression Analysis

The first analysis was performed for the patients who had TRUS results. Age, serum PSA level, serum free PSA level, percent of free/total PSA, prostate volume, PSA density, DRE result, TRUS result have selected as covariates. Summary of this analysis is shown in Table 30.

Table 30: Significant variables in logistic regression analysis of the patients who have TRUS result and fPSA level (n=721). Hosmer and Lemeshow Test, p= 0.187. B: Estimated coefficient. SE: Standard error.

Variable	B	SE	p	Odds	95% CI
Age	0.054	0.012	0.000	1.055	1.031-1.080
Free/total PSA	-0.017	0.008	0.048	0.983	0.967-1.000
PSA density	1.774	0.318	0.000	5.892	3.162-10,982
DRE	0.766	0.207	0.000	2.152	1.436-3.226
Constant	-5.409	0.791	0.000	0.004	-

The second analysis was performed adding the patients who had no TRUS results. Age, serum PSA level, serum free PSA level, percent of free/total PSA, DRE result have selected as covariates. Summary of this analysis is shown in Table 31.

The third analysis was performed adding the patients who had no fPSA levels. Age, serum PSA level, and DRE result have selected as covariates. Summary of this analysis is shown in Table 32.

Table 31: Significant variables in logistic regression analysis of the patients who have fPSA level (n=779). Hosmer and Lemeshow Test, p= 0.078

Variable	B	SE	p	Odds	95% CI
Age	0.047	0.011	0.000	1.048	1.026-1.072
PSA	0.051	0.010	0.000	1.052	1.032-1.073
Free/total PSA	-.0.024	0.008	0.003	0.976	0.961-0.992
DRE	0.827	0.191	0.000	2.287	1.574-3.323
Constant	-4.700	0.732	0.000	0.009	-

Table 32: Significant variables in logistic regression analysis of all patients (n=1090). Hosmer and Lemeshow Test, p= 0.206

Variable	B	SE	p	Odds	95% CI
Age	0.041	0.009	0.000	1.042	1.023-1.061
PSA	0.053	0.007	0.000	1.054	1.039-1.070
DRE	0.752	0.155	0.000	2.122	1.565-2.876
Constant	-4.695	0.602	0.000	0.009	-

ROC AUC comparison three LR sets is shown in Table 33.

Table 33: ROC AUC Comparison of three logistic regression sets.

Data	n	AUC	95% CI	p	Test Group AUC
Age, free/total PSA, PSA density, DRE	721	0.780	0.739-0.821	0.000	0.755
Age, PSA, free/total PSA, DRE	779	0.764	0.723-0.805	0.000	0.747
Age, PSA, DRE	1090	0.750	0.716-0.784	0.000	0.761

3.1.8. Artificial Neural Network

A design with three hidden nodes was used and 5300 iterations were performed. ROC AUC with the system is 0.746. At the level of 0.94 sensitivity, the system has 0.21 specificity. At the level of 0.95 sensitivity, the system has 0.17 specificity. The test group demonstrated 0.92 sensitivity and 0.21 specificity with an AUC of 0.562.

3.1.9. Decision Tree

Growing method is selected as CRT for the analysis. Decision tree in Figure 5 shows that the number of terminal nodes is 10. ROC AUC for decision probability is 0.759 (95 % CI 0.727-0.790, p=0.000). The test group showed similar results when the decision tree is applied (Table 34). ROC AUC of test group is 0.740 (p=0.000, 95% CI 0.686-0.794)

Table 34: Percent of malignant cases in each node for study and test groups.

Node	Study (%)	Test (%)	Total (%)
6	36	47	39
9	38	37	38
10	18	17	18
11	56	59	57
12	81	68	78
13	13	9	12
14	26	15	23
15	0	15	4
17	20	21	20
18	0	0	0

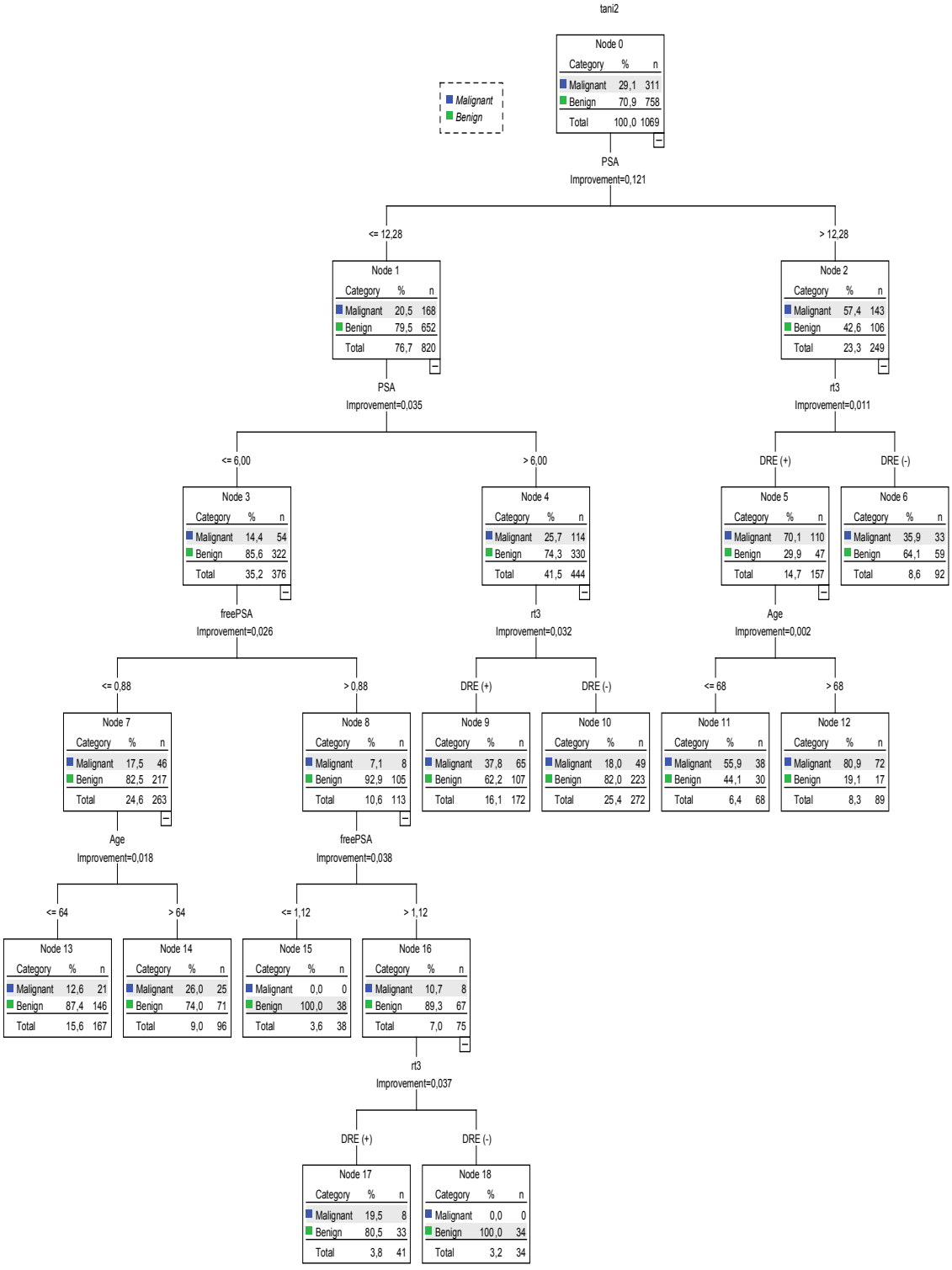

Figure 5: Decision tree for classification of cases.

3.1.10. Summary of Complex Approaches

Summary of complex approaches as comparison of ROC AUC's are shown in Table 35.

Table 35: Summary of complex approaches.

Method	AUC	Test AUC	Difference of AUC
LR1	0.780	0.755	-0.025
LR2	0.764	0.747	-0.017
LR3	0.750	0.761	0.011
ANN	0.746	0.562	-0.184
DT	0.759	0.740	-0.019

3.2. Analysis of High Grade Cases

3.2.1. Analysis of Overall PSA Results for High Grade Cases

The patients are classified according to prebiopsy serum PSA level. The results are shown in Table 36. The results of normal DRE and abnormal DRE patients are shown in Table 37 and Table 38.

Table 36: Proportion of high grade malignant cases.

PSA	Others	High grade	Total
0-2.5	168 (98.2%)	3 (1.8%)	171 (100.0%)
2.51-4	93 (96.9%)	3 (3.1%)	96 (100.0%)
4.01-6	236 (97.1%)	7 (2.9%)	243 (100.0%)
6.01-10	454 (93.2%)	33 (6.8%)	487 (100.0%)
Over 10	333 (73.0%)	123 (27.0%)	456 (100.0%)
Total	1284 (88.4%)	169 (11.6%)	1453 (100.0%)

Table 37: Proportion of high grade malignant cases in men with a normal DRE.

PSA	Others	High grade	Total
0-2.5	26 (96.3%)	1 (3.7%)	27 (100.0%)
2.51-4	19 (100.0%)	0 (0.0%)	19 (100.0%)
4.01-6	136 (100.0%)	0 (0.0%)	136 (100.0%)
6.01-10	285 (96.9%)	9 (3.1%)	294 (100.0%)
Over 10	163 (91.1%)	16 (8.9%)	179 (100.0%)
Total	629 (96.0%)	26 (4.0%)	655 (100.0%)

Table 38: Proportion of high grade malignant cases in men with an abnormal DRE

PSA	**Benign + low grade**	**High grade**	**Total**
0-2.5	142 (98.6%)	2 (1.4%)	144 (100.0%)
2.51-4	74 (96.1%)	3 (3.9%)	77 (100.0%)
4.01-6	100 (93.5%)	7 (6.5%)	107 (100.0%)
6.01-10	169 (87.6%)	24 (12.4%)	192 (100.0%)
Over 10	170 (61.4%)	107 (38.6%)	277 (100.0%)
Total	655 (82.1%)	143 (17.9%)	798 (100.0%)

Sensitivity and specificity levels for various PSA cut-off values are shown in table 39.

Table 39: High grade cases. Sensitivity and specificity levels for various PSA cut-off values.

PSA cut-off	**Overall**		**Normal DRE**		**Abnormal DRE**	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
2.5	0.98	0.13	0.96	0.04	0.99	0.22
4	0.96	0.20	0.96	0.07	0.97	0.33
6	0.92	0.39	0.96	0.29	0.92	0.48
10	0.73	0.74	0.62	0.74	0.75	0.74

3.2.2. PSA Density in High Grade

PSA densities in high grade and other patients are shown in Table 40.

Table 40: PSA density of high grade and benign+low grade patient groups.

Group	n	Median	Interquartile range	p
Benign+low grade	1212	0.21	0.20	0.000
High grade	156	0.70	1.43	
Total	1368	0.22	0.25	

When we take cut-off value of 0.26 to detect 84% of high grade cases (sensitivity is 0.84), specificity is 0.64 (Table 41).

Table 41: Distribution of cases when PSA density cut-off value is taken as 0.26 (p=0.000).

		PSA density				Total	
		< 0.26		>=0.26			
		n	%	n	%	n	%
Diagnosis	**Benign+low grade**	775	63.9	437	36.1	1212	100
	High grade	28	17.9	128	82.1	156	100
Total		803	58.7	565	41.3	1368	100

PSA density cut-off values for 0.90, 0.80, and 0.70 sensitivity levels are shown in Table 42.

Table 42: PSA density cut-off values for 0.98, 0.95, and 0.90 sensitivity levels.

PSA density cut-off level	Sensitivity	Specificity
0.10	0.98	0.16
0.13	0.95	0.27
0.18	0.90	0.42

Comparison of ROC AUC parameters of PSA and PSA density for high grade malignancy are shown in Table 43.

Table 43: Comparison of ROC AUC parameters of PSA and PSA density for high grade malignancy.

Variable	n	AUC	95% CI	p
PSA	1453	0.808	0.771-0.844	0.000
PSA density	1368	0.816	0.778-0.854	0.000

3.2.3. Age Specific Analysis

The patients divided into groups of 10 years (decades). Fifth decade is 40-49, 6^{th} decade is 50-59, 7^{th} decade is 60-69, and 8^{th} decade is 70-79 years old patients. Sensitivity and specificity values for different PSA cut-off values for each decade are shown in Table 44, Table 45, Table 46 and Table 47.

Table 44: Sensitivity and specificity levels for various PSA cut-off values in 5th decade patients (HG: high grade).

PSA	Under		Over		Total		Sensitivity	Specificity
	HG/total	%	HG/total	%	HG/total	%		
2.5	0/14	0.0	2/32	6.2	2/46	4.3	1.00	0.32
4	0/18	0.0	2/28	7.1	2/46	4.3	1.00	0.41
5	0/21	0.0	2/25	8.0	2/46	4.3	1.00	0.48
6	0/27	0.0	2/19	10.5	2/46	4.3	1.00	0.61
7	0/30	0.0	2/16	12.5	2/46	4.3	1.00	0.68
8	0/33	0.0	2/13	15.4	2/46	4.3	1.00	0.75
9	0/36	0.0	2/10	20.0	2/46	4.3	1.00	0.82
10	0/38	0.0	2/8	25.0	2/46	4.3	1.00	0.86

Table 45: Sensitivity and specificity levels for various PSA cut-off values in 6th decade patients (HG: high grade).

PSA	Under		Over		Total		Sensitivity	Specificity
	HG/total	%	HG/total	%	HG/total	%		
2.5	1/55	1.8	19/328	5.8	20/383	5.2	0.95	0.15
4	2/85	2.4	18/280	6.0	20/383	5.2	0.90	0.23
5	2/125	1.6	18/258	7.0	20/383	5.2	0.90	0.34
6	2/177	1.1	18/206	8.7	20/383	5.2	0.90	0.48
7	4/218	1.8	16/165	9.7	20/383	5.2	0.80	0.59
8	4/250	1.6	16/133	12.0	20/383	5.2	0.80	0.68
9	6/274	2.2	14/109	12.8	20/383	5.2	0.70	0.74
10	8/297	2.7	12/86	14.0	20/383	5.2	0.60	0.80

Table 46: Sensitivity and specificity levels for various PSA cut-off values in 7th decade patients (HG: high grade).

PSA	Under		Over		Total		Sensitivity	Specificity
	HG/total	%	HG/total	%	HG/total	%		
2.5	1/58	1.7	54/519	10.4	55/577	9.5	0.98	0.11
4	2/101	2.0	53/476	11.1	55/577	9.5	0.96	0.19
5	4/140	2.9	51/437	11.7	55/577	9.5	0.93	0.26
6	4/194	2.1	51/383	13.3	55/577	9.5	0.93	0.36
7	9/270	3.3	46/307	15.0	55/577	9.5	0.84	0.50
8	10/326	3.1	45/251	17.9	55/577	9.5	0.82	0.61
9	14/374	3.7	41/203	20.2	55/577	9.5	0.75	0.69
10	16/411	3.9	39/166	23.5	55/577	9.5	0.71	0.76

Table 47: Sensitivity and specificity levels for various PSA cut-off values in 8th decade patients (HG: high grade).

PSA	Under		Over		Total		Sensitivity	Specificity
	HG/total	%	HG/total	%	HG/total	%		
2.5	1/43	2.3	89/395	25.0	90/438	20.5	0.99	0.12
4	2/62	3.2	88/376	23.4	90/438	20.5	0.98	0.17
5	3/82	3.7	87/356	24.4	90/438	20.5	0.97	0.23
6	7/111	6.3	83/327	25.4	90/438	20.5	0.92	0.30
7	10/150	6.7	80/288	27.8	90/438	20.5	0.89	0.40
8	14/183	7.7	76/255	29.8	90/438	20.5	0.84	0.49
9	17/211	8.1	73/227	32.2	90/438	20.5	0.81	0.56
10	21/245	8.6	69/193	35.8	90/438	20.5	0.77	0.64

Comparison of ROC AUCs are shown in table 48.

Table 48: PSA ROC AUCs according to decades for high grade malignancy. CI: 95% Confidence interval.

Decade	**n**	**AUC**	**95% CI**	**p**
5th	45	0.977	0.933-1.000	0.024
6th	393	0.779	0.667-0.892	0.000
7th	577	0.806	0.739-0.873	0.000
8th	438	0.783	0.728-0.838	0.000
Overall	1453	0.808	0.771-0.844	0.000

3.2.4. Ratio of free/total PSA

Free PSA serum level is available in 1038 patients. Distribution of the cases according to 25% fPSA/PSA cut-off is shown in table 49. Sensitivity is 0.74 for 25% cut-off. Free/total PSA percent ROC AUC is shown in table 50.

Table 49: Distribution of the patients according to a cut-off of 25 % or less free PSA/PSA.

25% or less		**>25%**		p
High grade carcinoma/total	%	High grade carcinoma/total	%	
80/744	10.8	27/294	9.2	0.454

Table 50: ROC AUC's of free PSA and free/total PSA.

Patient group	n	AUC	CI	p
Free PSA	1038	0.764	0.714-0.814	0.000
Free/total PSA	1038	0.580	0.518-0.641	0.007

3.2.5. Summary by ROC AUCs of Classical Approaches for High Grade Malignancy

The highest AUC is seen in PSA in 5th decade. However, the cases in 5th decade is low (n=45). PSA density is the second and it has a low practical value because determination of it needs TRUS. PSA level is highest of the remaining parameters for PSA density (Table 51).

Table 51: Summary of ROC AUCs of classical approaches when applied to detect high grade tumours.

Variable	ROC AUC
PSA	0.808*
5th decade	0.977*
6th decade	0.779*
7th decade	0.806*
8th decade	0.783*
Free PSA	0.764*
PSA percent	0.580*
PSA density	0.822*

* indicates statistical significance from ROC AUC of 0.5.

3.2.6. Dynamic Concepts

In our patient group, previous PSA measures were available for 13 high grade 333 other cases. PSA velocity was median 0.46/year for benign and low grade cases and 1.63/year for high grade cases (p=0.536). PSA doubling time was median 2.2 years for benign and low grade cases and 1.0 years for high grade cases (p=0.094).

3.2.7 Logistic Regression Analysis

The analysis was also performed for high grade tumours. For the patients who had TRUS results, age, serum PSA level, serum free PSA level, percent of free/total PSA, prostate volume, PSA density, DRE result, TRUS result have selected as covariates. Summary of this analysis is shown in Table 52.

Table 52: Significant variables that show high grade in logistic regression analysis of the patients who have TRUS result and fPSA level (n=721). Hosmer and Lemeshow Test, p= 0.416

Variable	B	SE	p	Odds	95% CI
Age	0.068	0.018	0.000	1.071	1.035-1.108
PSA density	1.005	0.188	0.000	2.731	1.890-3,947
DRE	1.152	0.354	0.001	3.164	1.582-6.330
Constant	-8.107	1.209	0.000	0.000	-

The second analysis was performed adding the patients who had no TRUS results. Age, serum PSA level, serum free PSA level, percent of free/total PSA, DRE result have selected as covariates. Summary of this analysis is shown in Table 53.

Table 53: Significant variables that show high grade in logistic regression analysis of the patients who have fPSA level (n=779). Hosmer and Lemeshow Test, p= 0.671

Variable	B	SE	p	Odds	95% CI
Age	0.082	0.016	0.000	1.085	1.051-1.121
PSA	0.009	0.003	0.003	1.009	1.003-1.015
Free/total PSA	-.0.034	0.012	0.004	0.976	0.945-0.989
DRE	1.566	0.343	0.000	4.789	2.446-9.376
Constant	-8.219	1.138	0.000	0.000	-

The third analysis was performed adding the patients who had no fPSA levels. Age, serum PSA level, DRE result have selected as covariates. Summary of this analysis is shown in Table 54.

Table 54: Significant variables that show high grade in logistic regression analysis of all patients (n=1090). Hosmer and Lemeshow Test, p= 0.219

Variable	B	SE	p	Odds	95% CI
Age	0.067	0.013	0.000	1.069	1.042-1.097
PSA	0.019	0.004	0.000	1.019	1.012-1.027
DRE	1.507	0.283	0.000	4.512	2.591-7.858
Constant	-7.919	0.916	0.000	0.000	-

ROC AUC comparison three LR sets for high grade tumours is shown in Table 55.

Table 55: ROC AUC Comparison of three logistic regression sets for high grade tumours.

Data	n	AUC	95% CI	p	Test group AUC
Age, PSA density, DRE	721	0.839	0.799-0.880	0.000	0.784
Age, PSA, free/total PSA, DRE	779	0.813	0.762-0.863	0.000	0.739
Age, PSA, DRE	1090	0.822	0.781-0.863	0.000	0.772

3.2.8. Artificial Neural Network

The test repeated to detect high grade carcinomas. ROC AUC with the system is 0.721. At the level of 0.83 sensitivity, the system has 0.62 specificity. The test group demonstrated 0.81 sensitivity and 0.60 specificity with an AUC of 0.709.

3.2.9. Decision Tree

Growing method is selected as CRT for the analysis. Decision tree in Figure 6 shows that the number of terminal nodes is five. ROC AUC for decision probability is 0.818 (95% CI 0.772-0.864, p=0.000).

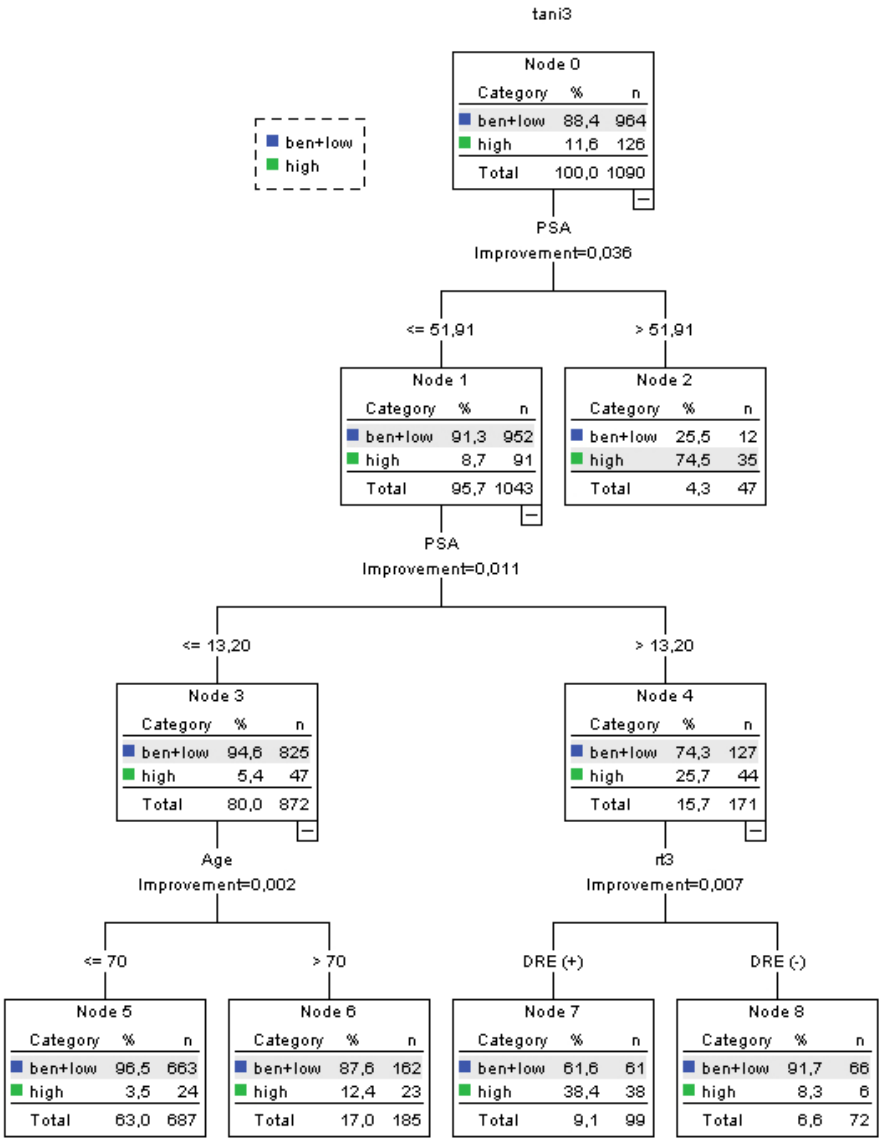

Figure 6: Decision tree for classification of high grade cases.

The test group showed similar results when the decision tree is applied (Table 56). ROC AUC of test group is 0.718 (p=0.000, 95% CI 0.626-0.811)

Table 56: Percent of high grade malignant cases in each node for study and test groups.

Node	Study (%)	Test (%)	Total (%)
2	75	65	72
5	4	6	4
6	12	9	11
7	38	23	34
8	8	12	10

3.2.10. Summary of Complex Approaches for Prediction of High Grade Carcinoma

Summary of complex approaches for prediction of high grade carcinoma is shown in Table 57.

Table 57: Summary of complex approaches for prediction of high grade carcinoma

Method	AUC	Test AUC	Difference of AUC
LR1	0.839	0.784	-0.055
LR2	0.813	0.739	-0.074
LR3	0.822	0.772	-0.050
ANN	0.721	0.709	-0.012
DT	0.818	0.718	-0.100

3.3. Analysis of the Cases whose PSA Level is Between 0 and 10

3.3.1. PSA Density

Prostate volume data is available for 946 patients. PSA densities in malignant and benign patients are shown in Table 58.

Table 58: PSA density of malignant and benign patient groups when PSA is between 0-10.

Group	n	Median	Interquartile range	p
Benign	764	0.16	0.13	0.000
Malignant	179	0.21	0.20	
Total	946	0.17	0.14	

PSA density cut-off values for 0.90, 0.80, and 0.70 sensitivity levels are shown in Table 59.

Table 59: PSA density cut-off values for 0.90, 0.80, and 0.70 sensitivity levels for cases whose serum PSA level is between 0 and 10.

PSA density cut-off level	Sensitivity	Specificity
0.09	0.90	0.19
0.12	0.80	0.32
0.15	0.70	0.44

ROC AUC parameters of PSA and PSA density are shown in Table 60.

Table 60: ROC AUC parameters of PSA and PSA density when serum PSA level is between 0 and 10.

Variable	**n**	**AUC**	**95% CI**	**p**
PSA	997	0.587	0.543-0.631	0.000
PSA density	946	0.625	0.577-0.673	0.000

3.3.2. Ratio of free/total PSA

Free PSA serum level is available in 750 patients. Distribution of the cases according to 25% fPSA/PSA cut-off is shown in table 61. Sensitivity is 0.71 for this level. Free PSA and Free/total PSA percent ROC AUC's are shown in table 62.

Table 61: Distribution of the patients according to a cut-off of 25% or less free PSA/PSA when serum PSA level is between 0 and 10.

25% or less		**>25%**		p
Carcinoma/total	%	Carcinoma/total	%	
94/512	18.4	38/238	16.0	0.423

3.3.3. Logistic Regression Analysis

The first analysis was performed for the patients who had TRUS results. Age, serum PSA level, serum free PSA level, percent of free/total PSA, prostate volume, PSA

density, DRE result, TRUS result have selected as covariates. Summary of this analysis is shown in Table 63.

Table 62: Free PSA and Free/total PSA ROC AUC when serum PSA level is between 0 and 10.

Variable	n	AUC	95% CI	p
Free PSA	750	0.540	0.487-0.593	0.149
Free/total PSA	750	0.560	0.504-0.616	0.031

Table 63: Variables in the equation by logistic regression analysis of the patients who have TRUS result and fPSA level (n=525) when serum PSA level is between 0 and 10. Hosmer and Lemeshow test p=0.947.

Variable	B	SE	p	Odds	95% CI
Age	0.033	0.015	0.024	1.034	1.004-1.064
PSA	0.120	0.060	0.046	1.128	1.002-1.270
PSA density	1.964	0.986	0.046	7.127	1.032-49.212
DRE	0.983	0.279	0.000	2.674	1.547-4.620
Constant	-5.407	0.975	0.000	0.004	-

The second analysis was performed adding the patients who had no TRUS results. Age, serum PSA level, serum free PSA level, percent of free/total PSA, DRE result have selected as covariates. Summary of this analysis is shown in Table 64.

Table 64: Significant variables in logistic regression analysis of the patients who have fPSA level (n=562) when serum PSA level is between 0 and 10. Hosmer and Lemeshow test p=0.325.

Variable	B	SE	p	Odds	95% CI
Age	0.025	0.014	0.074	1.025	0.998-1.054
PSA	0.216	0.048	0.000	1.241	1.130-1.364
DRE	1.048	0.256	0.000	2.851	1.725-4.711
Constant	-4.970	0.918	0.000	0.007	-

The third analysis was performed adding the patients who had no fPSA levels. Age, serum PSA level, DRE results have selected as covariates. Summary of this analysis is shown in Table 65.

Table 65: Significant variables in logistic regression analysis of all patients (n=756) when serum PSA level is between 0 and 10. Hosmer and Lemeshow test p=0.781.

Variable	B	SE	p	Odds	95% CI
Age	0.031	0.012	0.008	1.032	1.008-1.056
PSA	0.175	0.039	0.000	1.192	1.103-1.287
DRE	0.894	0.210	0.000	2.445	1.619-3.693
Constant	-4.973	0.779	0.000	0.007	-

ROC AUC comparison three LR sets is shown in Table 66.

Table 66: ROC AUC Comparison of three logistic regression sets when serum PSA level is between 0 and 10.

Data	n	AUC	95% CI	p	Test group AUC
Age, PSA density, DRE	525	0.678	0.625-0.731	0.000	0.717
Age, PSA, free/total PSA, DRE	562	0.660	0.608-0.712	0.000	0.656
Age, PSA, DRE	756	0.661	0.609-0.712	0.000	0.662

3.3.4. Artificial Neural Network

A design with three hidden nodes were used and 5300 iterations were performed. ROC AUC with the system is 0.644. When the cut-of value is taken as 0.2, the system has 0.95 sensitivity and 0.33 specificity. However, test group failed to show a statistically significant ROC AUC.

3.3.5. Decision Tree Analysis by CRT Algorithm

Decision tree in Figure 7 shows that the number of terminal nodes is seven. ROC AUC for decision probability is 0.698 (95% CI 0.653-0.743, p=0.000).

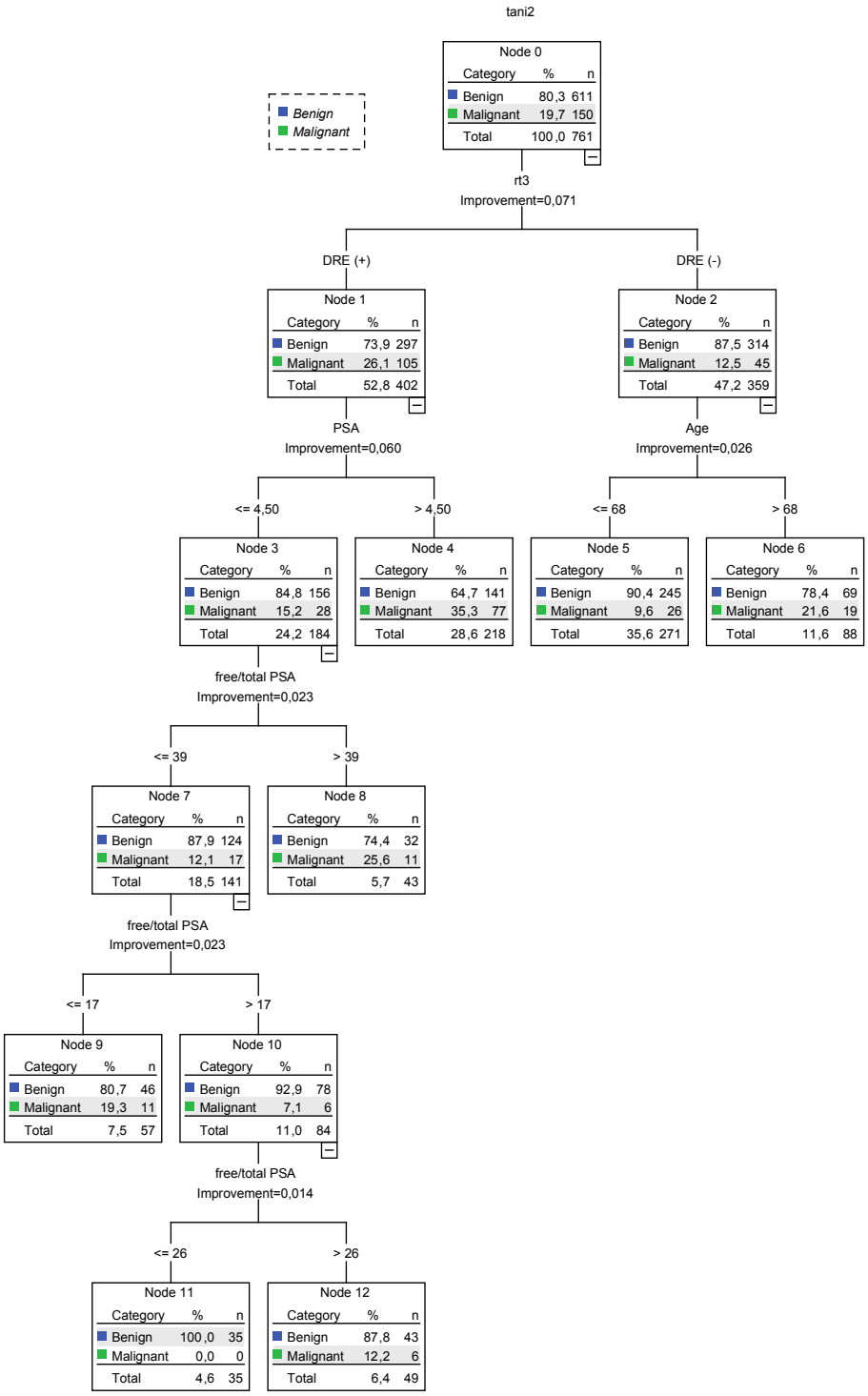

Figure 7: Decision tree of cases whose serum PSA level is between 0 and 10.

The test group showed similar results when the decision tree is applied (Table 67). ROC AUC of test group is 0.629 (p=0.008, 95% CI 0.536-0.721)

Table 67: Percent of malignant cases in each node for study and test groups.

Node	Study (%)	Test (%)
4	35	31
5	10	15
6	22	25
8	26	7
9	19	17
11	0	0
12	12	9

3.3.6. Decision Tree Analysis by QUEST Algorithm

The patients who have fPSA result (750 patients) have been selected for further evaluation by QUEST algorithm. The patients randomly split into study (n=562) and validation (test) (n=188) groups. The mean age and standard deviation of the study group were 62.7 and 8.3 years respectively. The median PSA level in this group was 5.65 ng/mL. The median free PSA level was 0.95 ng/mL. DRE was normal in 47.5% of patients, suspicious in 15.3% of patients, and positive in 37.2% of patients. Cancer was detected 98 (17.4%) of patients and 21 (3.2%) of the cases were high grade malignant (Gleason grade ≥7).

QUEST algorithm identified the following five nodes (groups) having different levels of cancer probability (Figure 8): (1) PSA more than 5.98 ng/mL; (2) PSA ≤

5.98 ng/mL and DRE is suspicious or positive; (3) PSA ≤ 5.98 ng/mL and DRE is negative and free PSA more than 0.81; (4) PSA ≤ 5.98 ng/mL and DRE is negative and free PSA ≤ 0.81 and age ≤ 57 years; (5) PSA ≤ 5.98 ng/mL and DRE is negative and free PSA ≤ 0.81 and age more than 57 years. The incidences of cancer detection in these groups were 25%, 15%, 0%, 4% and 16%, respectively. If the nodes 3 and 4 were considered as negative, the system would detect 97 of 98 cancer cases with 0.99 sensitivity, saving 74 patients from biopsy (13% of the patients).

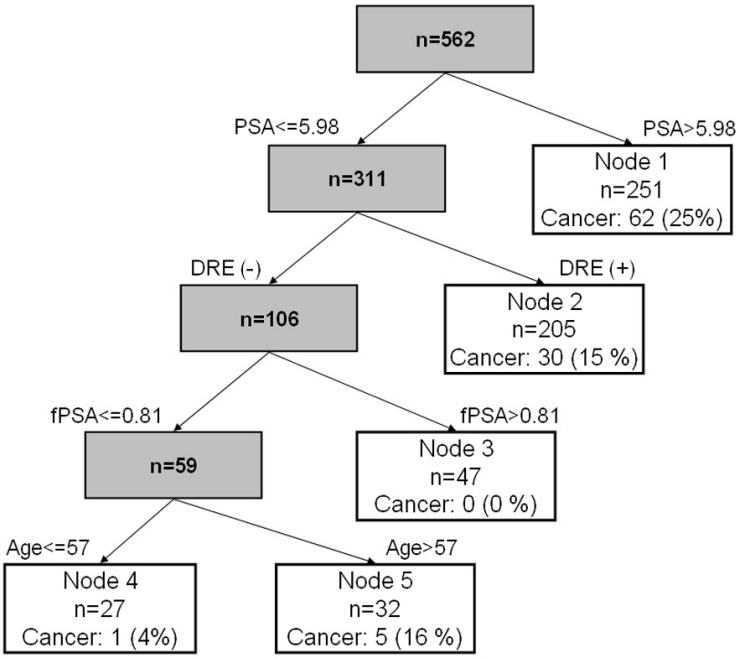

Figure 8: Decision tree obtained by QUEST analysis.

The analysis was then carried out using the randomly selected validation set (n=188). In validation set, the sensitivity was 0.97 (35 of 36 patients). Comparison of study group and validation group is shown in Table 68. Node 3 contained cancer cases neither in study nor in validation group. Node 4 had two cancer patients, one in each group. These two patients were Gleason grade 5 and 6.

Table 68: Comparison of results of decision tree in study and validation groups.

Node	Study group		Validation group		Total	
	cancer/total	%	cancer/total	%	cancer/total	%
1	62/251	25	22/98	22	84/349	24
2	30/205	15	11/58	19	41/263	16
3	0/47	0	0/14	0	0/61	0
4	1/27	4	1/7	14	2/34	6
5	5/32	16	2/11	18	7/41	17
Total	98/562	17	36/188	19	134/750	18

The results generated by the QUEST were then compared with a logistic regression model created using the same factors. The decision tree had a ROC curve AUC of 0.62 (95% confidence interval 0.58-0.68). When the same variables were entered into the logistic regression model, age (p=0.036), DRE (p=0.001) and PSA (p=0.001) were detected as statistically significant variables. The AUC of LR was 0.68 (95% confidence interval 0.63-0.73). The AUC of free PSA/PSA ratio alone was calculated as 0.56 (95% confidence interval 0.50-0.62). The AUC's above were obtained using the complete data set.

3.3.7. Summary of Various Methods for Prediction of Carcinoma when PSA is 0-10.

Summary of various methods for prediction of carcinoma when PSA is 0-10 are shown in Table 69.

Table 69: Summary of various methods for prediction of carcinoma when PSA is 0-10.

Method	AUC	Test AUC	Difference of AUC
PSA	0.587		
PSA Density	0.625	-	-
Free PSA	0.540	-	-
Free/total PSA	0.560	-	-
LR1	0.678	0.717	0.039
LR2	0.660	0.656	-0.004
LR3	0.661	0.662	0.001
ANN	0.644	NS	-
DT	0.698	0.629	-0.069

3.4. Examination of the High Grade Carcinoma in Cases whose Serum PSA Level is Between 0 and 10

3.4.1. PSA Density

Prostate volume data is available for 946 patients. PSA densities in high grade malignant and other patients are shown in Table 70.

Table 70: PSA density of high grade malignant and other cases.

Group	n	Median	Interquartile range	p
Benign+low grade	898	0.17	0.14	0.000
High grade malignant	45	0.28	0.24	
Total	943	0.17	0.14	

PSA density cut-off values for 0.90, 0.80, and 0.70 sensitivity levels are shown in Table 71.

Table 71: PSA density cut-off values for 0.90, 0.80, and 0.70 sensitivity levels for cases whose serum PSA level is between 0 and 10.

PSA density cut-off level	Sensitivity	Specificity
0.05	0.98	0.07
0.09	0.95	0.18
0.12	0.90	0.29

ROC AUC parameters of PSA and PSA density are shown in Table 72.

Table 72: ROC AUC parameters of PSA and PSA density.

Variable	n	AUC	95% CI	p
PSA	997	0.647	0.569-0.724	0.001
PSA density	943	0.686	0.600-0.771	0.000

3.4.2. Ratio of free/total PSA

Free PSA serum level is available in 750 patients. Distribution of the cases according to 25 % fPSA/PSA cut-off is shown in table 73. Sensitivity is 0.64 for 25% cut-off. Free PSA and Free/total PSA percent ROC AUC's are shown in table 74.

Table 73: Distribution of the patients according to a cut-off of 25 % or less free PSA/PSA.

25% or less		**>25%**		p
High grade carcinoma/total	%	High grade carcinoma/total	%	
18/512	3.5	10/238	4.2	0.645

Table 74: Free PSA and Free/total PSA ROC AUC.

Variable	**n**	**AUC**	**95% CI**	**p**
Free PSA	750	0.594	0.490-0.698	0.092
Free/total PSA	750	0.529	0.409-0.649	0.603

3.4.3. Logistic Regression Analysis for Prediction of High Grade Cases

The first analysis was performed for the patients who had TRUS results. Age, serum PSA level, serum free PSA level, percent of free/total PSA, prostate volume, PSA density, DRE result, TRUS result have selected as covariates. Summary of this analysis is shown in Table 75.

Table 75: Variables in the equation by logistic regression analysis of the patients who have TRUS result and fPSA level (n=525). Hosmer and Lemeshow test p=0.267.

Variable	**B**	**SE**	**p**	**Odds**	**95% CI**
Age	0.062	0.028	0.025	1.064	1.008-1.123
PSA density	3.440	1.061	0.001	31.196	3.901-249.506
Constant	-8.016	1.916	0.000	0.000	-

The second analysis was performed adding the patients who had no TRUS results. Age, serum PSA level, serum free PSA level, percent of free/total PSA, DRE result have selected as covariates. Summary of this analysis is shown in Table 76.

Table 76: Significant variables in logistic regression analysis of the patients who have fPSA level (n=562).

Variable	B	SE	p	Odds	95% CI
PSA	0.267	0.093	0.004	1.306	1.087-1.568
DRE	1.273	0.506	0.012	3.571	1.324-9.629
Constant	-5.621	0.805	0.000	0.004	-

The third analysis was performed adding the patients who had no fPSA levels. Age, serum PSA level, DRE result have selected as covariates. Summary of this analysis is shown in Table 77.

Table 77: Significant variables in logistic regression analysis of all patients (n=756). Hosmer and Lemeshow test p=0.845.

Variable	**B**	**SE**	**p**	**Odds**	**95% CI**
Age	0.045	0.022	0.044	1.046	1.001-1.093
PSA	0.266	0.078	0.001	1.305	1.120-1.520
DRE	1.161	0.417	0.005	3.193	1.410-7.232
Constant	-8.375	1.504	0.000	0.000	-

ROC AUC comparison three LR sets is shown in Table 78.

Table 78: ROC AUC Comparison of three logistic regression sets.

Data	n	AUC	95% CI	p	Test group AUC
Age, PSA density, DRE	525	0.740	0.655-0.825	0.000	0.690
Age, PSA, free/total PSA, DRE	562	0.744	0.661-0.827	0.000	0.786
Age, PSA, DRE	756	0.756	0.675-0.838	0.000	0.789

3.4.4. Artificial Neural Network

A design with three hidden nodes was used and 5300 iterations were performed. ROC AUC with the system is 0.741. When the cut-of value is taken as 0.02, the system has 0.95 sensitivity and 0.33 specificity.

3.4.5. Decision Tree

Growing method is selected as CRT for the analysis. Decision tree in Figure 9 shows that the number of terminal nodes is six. ROC AUC for decision probability is 0.770 (95% CI 0.710-0.831, p=0.000).

The test group showed similar results when the decision tree is applied (Table 79). ROC AUC of test group is 0.725 (p=0.030, 95% CI 0.573-0.877)

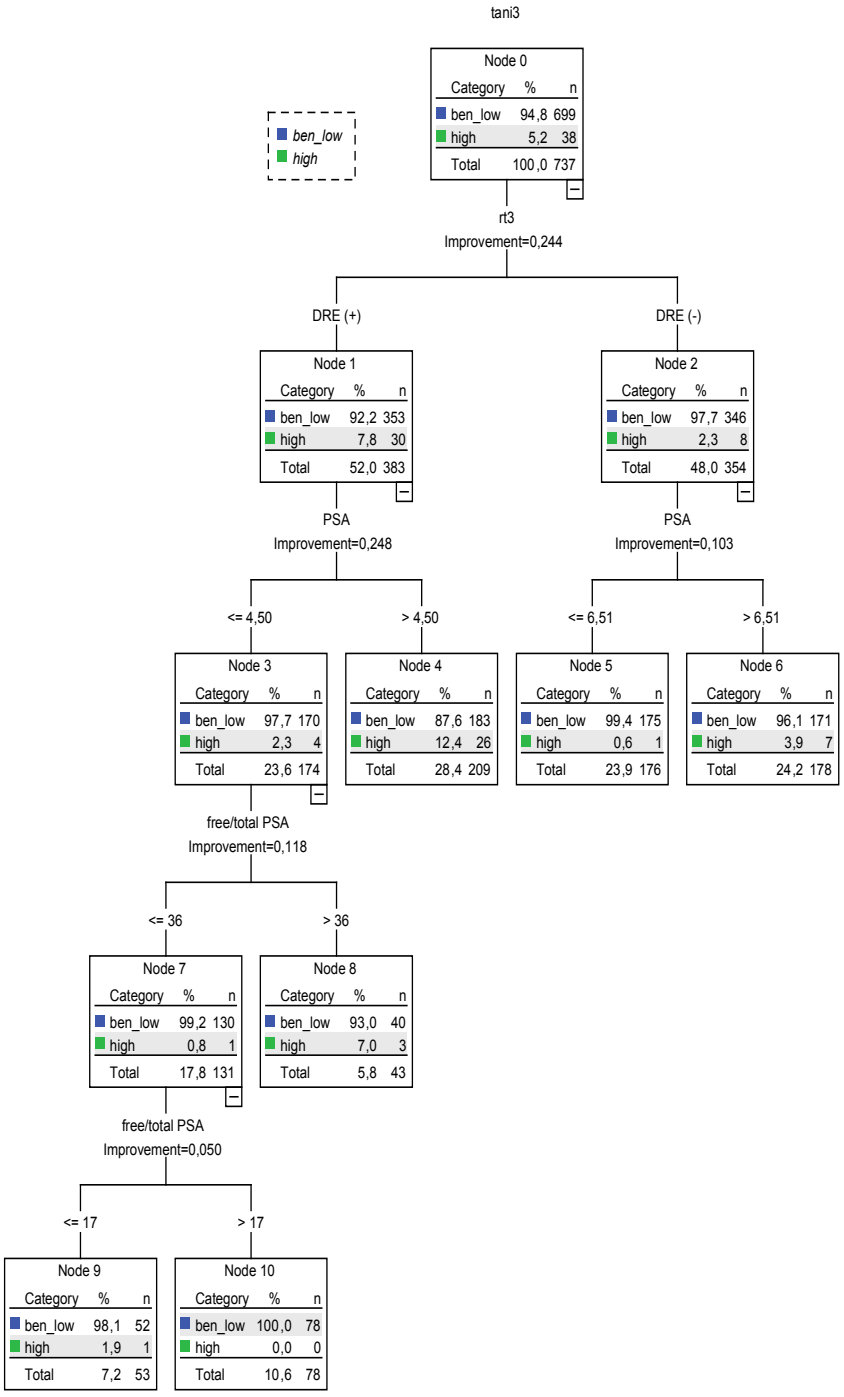

Figure 9: Decision tree of high grade cases whose serum PSA level is between 0 and 10.

Table 79: Percent of malignant cases in each node for study and test groups.

Node	Study (%)	Test (%)
4	12	8
5	1	0
6	4	3
8	7	0
9	2	6
10	0	0

3.4.6. Summary of Applied Methods for Prediction of High Grade Carcinoma when PSA is 0-10.

Summary of applied methods for prediction of high grade carcinoma when PSA is 0-10 is shown in Table 80.

3.5. Analysis of Cases whose PSA Level is over 10

3.5.1. Logistic Regression Analysis for Prediction of Malignant Cases

Age, serum PSA level, and DRE result have selected as covariates. Summary of this analysis is shown in Table 81.

Table 80: Summary of applied methods for prediction of high grade carcinoma when PSA is 0-10.

Method	AUC	Test AUC	Difference of AUC
PSA	0.647	-	-
PSA density	0.686	-	-
Free PSA	0.594	-	-
Free/total PSA	0.529	-	-
LR1	0.740	0.690	-0.050
LR2	0.744	0.786	0.042
LR3	0.756	0.789	0.033
ANN	0.741	Not significant	-
DT	0.770	0.725	-0.045

Table 81: Significant variables in logistic regression analysis of patients who have a PSA level over 10 (n=334). Hosmer and Lemeshow test p=0.740.

Variable	B	SE	P	Odds	95% CI
Age	0.039	0.016	0.013	1.039	1.008-1.071
PSA	0.030	0.008	0.000	1.031	1.015-1.046
DRE	1.003	0.257	0.000	2.727	1.650-4.509
Constant	-4.015	1.064	0.000	0.018	-

ROC AUC comparison of LR in study and test groups shown in Table 82.

Table 82: ROC AUC comparison of LR in study and test groups for cases whose serum PSA level is over 10.

Data	AUC	95% CI		p
		Lower bound	Upper bound	
Study	0.764	0.713	0.814	0.000
Test	0.697	0.604	0.789	0.000

3.5.2. Logistic regression analysis for prediction of high grade cases

Age, serum PSA level, and DRE result have selected as covariates. Summary of this analysis is shown in Table 83.

Table 83: Significant variables in logistic regression analysis of patients who have a PSA level over 10 (n=334). Hosmer and Lemeshow test p=0.181.

Variable	B	SE	p	Odds	95% CI
Age	0.055	0.019	0.003	1.056	1.018-1.095
PSA	0.007	0.002	0.003	1.007	1.002-1.011
DRE	2.271	0.414	0.000	9.686	4.299-21.825
Constant	-6.642	1.336	0.000	0.001	-

ROC AUC comparison of LR in study and test groups are shown in Table 84.

Table 84: ROC AUC comparison of LR in study and test groups.

Data	AUC	95% CI		p
		Lower bound	Upper bound	
Study	0.809	0.760	0.858	0.000
Test	0.690	0.575	0.805	0.002

3.6. Genetic Algorithm

Analysis of the patients who have PSA values between 4 and 10 by genetic algorithm has produced the following rule: If PSA is over 4.5 and DRE is positive and PSA density over 0.142, the patient is likely to have cancer. Using this criterion, sensitivity is 0.58 and specificity is 0.78 in the data set. ROC AUC is 0.671(95% CI: 0.604-0.737 p=0.000) by this method. The rule has been also applied to test group.

On the same data set, according to LR, age, PSA density and DRE are significant in the prediction of malignancy with an ROC AUC of 0.718 (95% CI: 0.658-0.778, p=0.000).

3.7. Final Prediction Algorithms

As seen in Table 35 and Table 57, the most successful models for the prediction of prostate cancer are LR and DT. We prepared two hybrid models using both of these models, one for cancer, and the other for high grade cancer. First, we have determined the nodes which give very high possibilities and very low possibilities in DTs. After the cases in these nodes were removed, the remaining cases were further analysed by LR. For carcinoma algorithm, any probability over 50% was regarded as "High probability", any probability below 1% was regarded as "Low probability". For high grade carcinoma algorithm, any probability over 20% was regarded as "High probability", any probability below 1% was regarded as "Low probability.

For LR analysis of carcinoma, after nodes 11, 12, and 18 removed from data set, 1197 cases have remained. Result of LR is shown in Table 85.

Table 85: Significant variables in logistic regression analysis of the patients who have been remained after elimination of DT cases (n=1197). Hosmer and Lemeshow Test, p= 0.332

Variable	**B**	**SE**	**p**	**Odds**	**95% CI**
Age	0.037	0.009	0.000	1.037	1.019-1.055
PSA	0.080	0.012	0.000	1.084	1.058-1.110
DRE	0.718	0.160	0.000	2.050	1.497-2.807
Constant	-4.608	0.580	0.000	0.010	-

The final decision algorithm for cancer is presented in Figure 10. The formula which will be applied in this algorithm is;

Probability of Prostate Ca=1/[1+exp[-(-4,608+age*0,037+PSA*0,08+DRE*0.718)]

(Equation 3)

Where DRE is 1 in case of being pathologic, 0 in case of being normal.

For LR analysis of high grade carcinoma, after nodes 2 and 7 removed from data set, 1246 cases have remained. Result of LR is shown in Table 86.

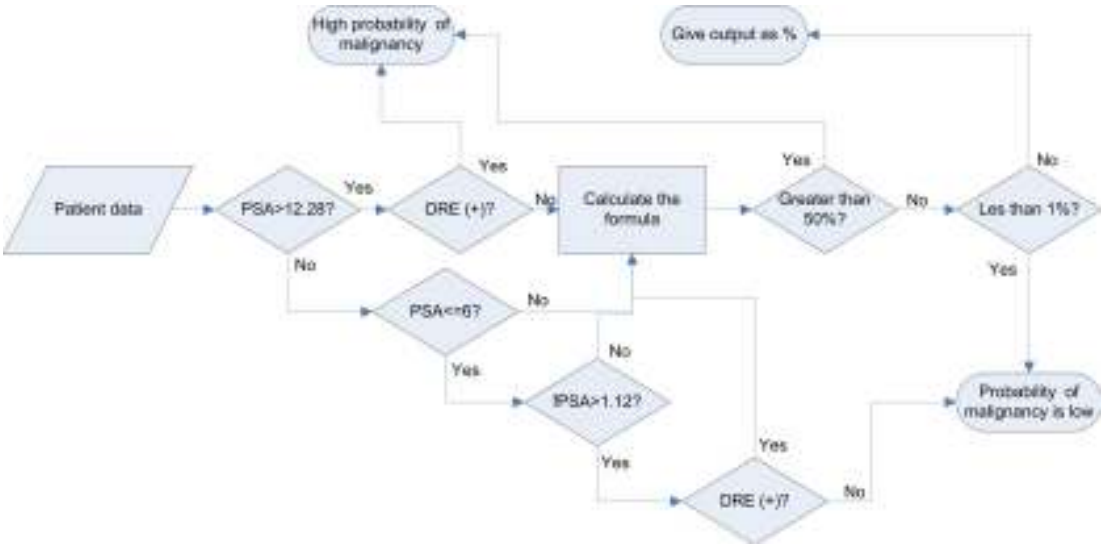

Figure 10: The final prediction decision algorithm for cancer.

Table 86: Significant variables in logistic regression analysis of the patients who have been remained after elimination of DT cases (n=1246). Hosmer and Lemeshow Test, p= 0.622

Variable	**B**	**SE**	**p**	**Odds**	**95% CI**
Age	0.055	0.015	0.000	1.056	1.025-1.089
PSA	0.090	0.017	0.000	1.094	1.058-1.131
DRE	1.309	0.306	0.000	3.704	2.033-6.750
Constant	-7.909	1.051	0.000	0.000	-

The final decision algorithm for high grade cancer is presented in Figure 11. The formula which will be applied in this algorithm is;

Probability of Prostate Ca=1/[1+exp[-(-7,909+age*0,055+PSA*0,09+DRE*1.309)]

(Equation 4)

Where DRE is 1 in case of being pathologic, 0 in case of being normal.

Additional rules were needed for of consistency between these two algorithms;

1- If probability of carcinoma is low, then leave high grade carcinoma output empty.

2- If high grade carcinoma probability is higher than carcinoma probability, write high grade carcinoma probability to carcinoma probability.

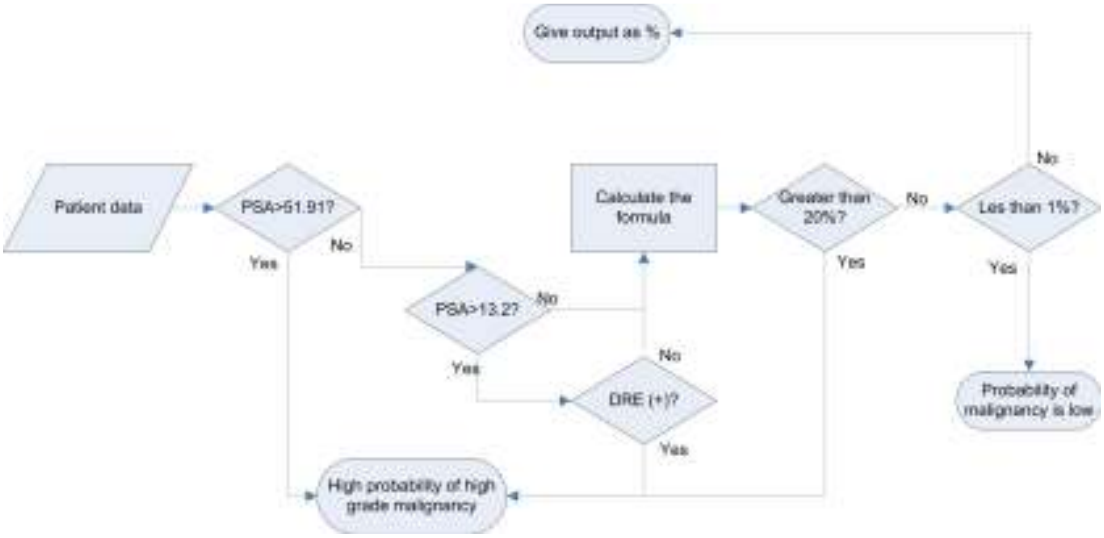

Figure 11: The final prediction decision algorithm for high grade cancer.

3.8 Analysis of Final Algorithms

ROC AUC parameters for hybrid algorithms are presented in Table 87.

When algorithm for carcinoma is applied to our data set, the probability of malignancy is very low for 33 patients. These patients would be saved from biopsy.

They constitute 2.3% of all patients and 4.4% of the patients whose PSA is below 10, without a loss from sensitivity.

Table 87: ROC AUC parameters of hybrid algorithms for carcinoma and high grade carcinoma.

Algorithm	n	AUC	95% CI	p
Carcinoma	1453	0.758	0.729-0.786	0.000
High grade carcinoma	1453	0.841	0.808-0.873	0.000

3.9. User Interface

An easy to use interface designed for the users. The main page is presented in Figure 12. A user questionnaire were also present in web site (Figure 13).

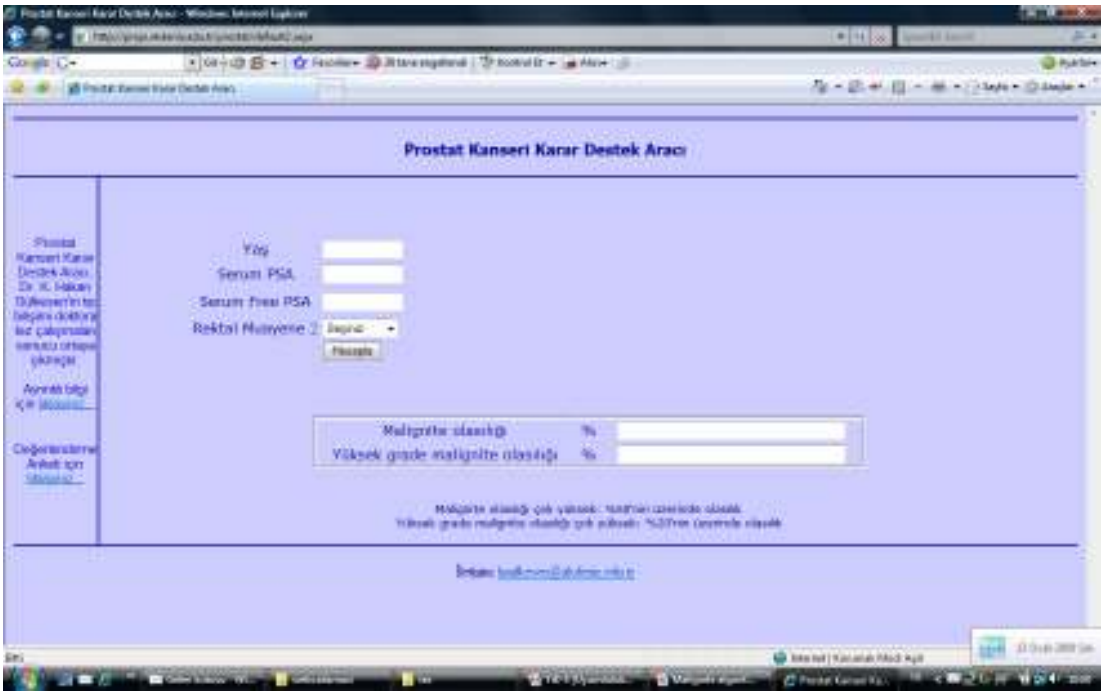

Figure 12: Main page of decision support tool.

Figure 13: User questionnaire on the web.

3.10. Results of the User Questionnaire

Fifty urologists have completed the questionnaire on the web. Their age was 39.6±9.2 (mean±standard deviation). The users were from 12 different cities, and 23 different hospitals. Twenty eight (56%) of the users were from university hospitals, and the remaining practitioners were working in state or private hospitals. Sixteen (32%) of them were residents, 18 (36%) were specialists and 16 (32%) were academics. The respondents were using computers for 16.1±11.5 hours a week, and no significant correlation has been observed (r=-.261, P=.068) between the age of the users and the duration of computer use.

Respondents stated their level of agreement with 15 statements by using five-point Likert scale (i.e. 5=Strongly Agree, 4=Agree, 3= Not sure, 2=Disagree, 1=Strongly Disagree, Table 88). An estimate of the internal consistency of this scale yielded a coefficient alpha of .770, which indicates that participants responded consistently across all items.

Table 88. Answers of the urologists to Likert type questions.

Question	Strongly disagree	Disagree	Not sure	Agree	Strongly agree	n
1. Computers should be used to support decisions in healthcare	0 (0%)	0 (0%)	1 (2%)	22 (44%)	27 (54%)	50 (100%)
2. Computers increase the efficiency of the physician	1 (2%)	1 (2%)	11 (22%)	19 (38%)	18 (36%)	50 (100%)
3. Computers help in making correct decisions in healthcare	0 (0%)	3 (6%)	4 (8%)	30 (60%)	13 (26%)	50 (100%)
4. The results of the system are consistent	0 (0%)	1 (2%)	18 (36%)	28 (56%)	3 (6%)	50 (100%)
5. The results of the system are not suitable for our patients	8 (16%)	19 (38%)	19 (38%)	4 (8%)	0 (0%)	50 (100%)
6. The results of the system are correct	0 (0%)	1 (2%)	22 (46%)	23 (48%)	2 (4%)	48 (100%)
7. Use of the system is not practical	6 (12%)	26 (52%)	14 (28%)	3 (6%)	1 (2%)	50 (100%)
8. I would have difficulty finding time to use this system	7 (14%)	23 (46%)	12 (24%)	6 (12%)	2 (4%)	50 (100%)
9. In my opinion, the system is useful in clinical practice	1 (2%)	1 (2%)	12 (24%)	31 (62%)	5 (10%)	50 (100%)
10. Use of the system is easy	0 (0%)	1 (2%)	9 (18%)	27 (55%)	12 (24%)	49 (100%)
11. Inputs of the system are not sufficient	3 (6%)	14 (29%)	18 (37%)	10 (20%)	4 (8%)	49 (100%)
12. There is a need for such a system in daily clinical practice	1 (2%)	3 (6%)	9 (18%)	24 (48%)	13 (26%)	50 (100%)
13. The system may be used for educational purposes	0 (0%)	5 (10%)	5 (10%)	30 (60%)	10 (20%)	50 (100%)
14. I could use such a system if it is further developed	0 (0%)	0 (0%)	6 (12%)	33 (66%)	11 (22%)	50 (100%)
15. I could share the results of the system with interested patients	1 (2%)	3 (6%)	7 (14%)	33 (66%)	6 (12%)	50 (100%)

The first three statements were asked to ascertain the general attitude of the respondents to use of computers in healthcare. On a five graded scale, means of the answers to the first three questions were taken to calculate attitude to computer use in healthcare (ACH) score. Mean ACH was 4.2 (minimum: 3.3, maximum: 5). Duration

of computer use and ACH have shown a positive correlation (p=0.003, Table 89). Age has shown no relation to ACH (p=0.522).

The next eight statements (4-11) were related to opinions about the decision support tool. The Mean opinion score (Attitude to Decision Support Tool; ADST) was 3.7 (1: completely negative, 5: completely positive). The opinions about decision support tool showed no correlation with age (p=0.813) or duration of computer use (p=0.809), but there was a positive correlation with ACH (p=0.013, Table 89). The result of one of the questions related to tool (8th question), "I would have difficulty finding time to use this system" was interesting. Eight (16%) of the users agreed or definitely agreed it would be difficult to find time to use the tool. Another 12 (24%) were not sure that they would find time. The question has shown an inverse relationship with ACH (r=-0.448, p=0.001). No relation has been observed with age (r=-0.021, p=0.888), or duration of computer use (r=-0.120, p=0.408).

The twelfth question was asked to ascertain the physician's opinion about the need for using a decision support tool in biopsy decision. Thirty seven (74%) of them agreed or strongly agreed on the need for such a tool. Nine (18%) were unsure about the need and only four (8%) negative responses were received. ACH has shown positive correlation with the need for the decision support tool (p=0.009). ADST (p=0.126), age (p=0.197) and duration of computer use (p=0.817) has shown no relation with this statement (Table 89). Residents scored 3.5±0.9 and specialists scaled 4.1±0.9 for the need (p=0.040).

The majority of users (80%) have agreed or strongly agreed on the use of the tool for educational purposes, five (10%) of them were not sure for educational use, and five (10%) expressed a negative opinion about it. The answer to this question has shown no relation with age, computer use, ACH, or ADST.

Question 14 was asked to find out if the users would use the tool if it was further developed. Forty four (88%) users agreed or strongly agreed to use the tool in the case of further development. Six (12%) were not sure, and no negative response was

present. The answer to this question showed positive correlation with ACH (p=0.001) but no significant correlation was observed with ADST (p=0.056), age (p=0.096), or computer use (p=0.099, Table 89).

Table 89: Correlation coefficients between the variables in the questionnaire. ACH: Attitude to computer use in healthcare; ADST: Attitude to decision support tool; DS: Decision Support; *: *p*<.05; **: p<.01.

	Duration of computer use	ACH	ADST	Need of DS tool	Use in Education	Use in case of Developed	Share the results with patients	Future use intention
Age	.261	-.093	-.034	.186	.117	-.238	-.156	-.238
Duration of computer use	-	.416*	-.035	-.034	-.033	.236	.008	.236
ACH	-	-	.351*	.367**	-.058	.459**	.310*	.272
ADST	-	-	-	.219	-.237	.272	.324	.401**

Question 15 was asked to learn the opinion of the physicians about sharing the system's outputs with patients. Thirty nine (78%) of them said they would share, seven (14%) were not sure and four (8%) of them expressed a negative opinion about it. The answer to this question has shown a positive correlation with ACH (p=0.029) and ADST (p=0.022), but no significant correlation was observed with age (p=0.278) and computer use (p=0.957, Table 89).

One additional question was asked to evaluate future use intention of the users. One of them (2%) has chosen "I do not use this system". 13 (26%) of them have chosen "I occasionally use the system", 16 (32%), 15(30%), and 5 (10%) of them have chosen "I use it when I have difficulty in making a biopsy decision", "I use it frequently" and "I use it for every patient" respectively. The answers to this question have shown positive correlation with ADST (P=.004), but no significant correlation

was observed with age (p=0.183), computer use (p=0.569) or ACHS (p=0.111, Table 89).

The users were also requested to share their opinions and suggestions. Fourteen of the users expressed opinions or suggestions. Their statements can be seen in Table 90.

Table 90: Opinions and suggestions of the users about online prostate biopsy decision support tool.

n	**Statement**
3	Increasing the number of inputs would improve the quality of the output
2	The system needs to be improved
1	The system does not give importance to high PSA in young patients
1	The system is not for the physicians, but for the patients
1	I think the results are not in concordance with medical literature
1	Nomograms for prediction of prostate cancer have been available for a long time but have not entered clinical practice
1	Before answering the questionnaire, I would like to see the data and statistical analysis related to the algorithm
1	I would prefer to evaluate it after longer use
1	Useful for routine evaluation of the patient and clinical education
1	It is easy to use
1	To avoid unnecessary biopsies, this similar studies are needed

CHAPTER 4

DISCUSSION

Prediction studies on prostate cancer by the help of PSA is important because PSA is the first serum marker which can be used in cancer screening and the experiences from these studies can be used in future possible cancer markers. In spite of importance of prediction of prostate cancer problem, there were no studies evaluating a wide range of methods on the same data set. Additionally, the problem was not studied in Turkish Population in detail.

The present study included 1453 biopsied patients. The number of the patients is highest in the Turkish studies and quite sufficient compared to international series. However, the number of the cases would be higher if the patient records were more carefully entered. Some vital data such as serum PSA level or biopsy result were absent in the files, so several hundreds of patients had been excluded from the study. A small fraction of the patients in the included data set were deficient of TRUS data, in spite of all of them were biopsied by the help of TRUS. The strong aspect of the study is being reflective of a geographic region, Antalya district, because near all the patients in the region was referred to Akdeniz University Hospital which had only TRUS centre in the region during the study period.

In this study, analysis of the cases whose PSA level is between 0 and 10 were also performed because it is widely accepted that a substantial percent of the patients are malignant if PSA is over 10 and biopsy has to be performed in these patients. The main problem is in 0-10 range and further evaluation of these patients may reveal useful results.

According to Western studies, carcinoma rate is 10-20%, 25%, and 50-60% for serum PSA levels 2.5-4, 4-10, and over 10 respectively in DRE negative patients (Schmid, et al., 2004). The corresponding rates in our study were 11%, 14%, and 34%. The incidence of the disease is lower in country (Fidaner, et al., 2001), and the rates reflect the effect of incidence. However, malignancy rate is unexpectedly high (11%) in 0-2.5 range, in contrast to previous studies which reports a rate under 2% (Roscigno, et al., 2004). The reason of this result is possibly the effect of absence of screening in our country. The patients in this range must be clinically symptomatic cases who admitted to physician by obstructive symptoms.

The classical threshold for PSA is 4 ng/ml. According to this cut-off, the sensitivity is 0.92 in our patients. This figure is 0.96 for DRE negative patients, and 0.90 for DRE positive patients. This level is quite higher than reported 0.70-0.80 sensitivity levels (Roscigno, et al., 2004). The discussions about lowering the limit to 2.5 ng/dl may not be appropriate for Turkish population. Analysis of results for high grade cases showed that the high grade carcinoma rates were 2%, 3%, 7% and 27% in PSA levels 0-2.5, 2.5-6, 6-10 and over 10 respectively. In DRE negative patients, corresponding rates were 4%, 0%, 3% and 9% respectively.

In our study, sensitivity and specificity for a PSA level greater than 4 ng/mL was 0.92 and 0.27 respectively. In a meta-analysis of similar Korean studies (Song, Kim, Chung, & Kane, 2005) the corresponding values were 0.91 and 0.36. Sensitivity level is very close in both studies, but our specificity level is substantially lower than the Korean meta-analysis, which may reflect lower incidence of prostatic carcinoma in our country. Another meta-analysis of screening studies from various countries (Mistry & Cable) reported 0.72 sensitivity and 0.93 specificity. These figures are

quite different from our results or Korean results, reflecting the effect of difference in the way of patient selection by screening.

PSA levels show correlation with age and prostate volume as shown in literature (Richardson & Oesterling, 1997).

Because complexed PSA and isoenzymes of free PSA are not studied routinely in our centre, we could not evaluate the value of these tests.

PSA density

PSA density in malignant patients is median 0.39. The corresponding value in benign patients was 0.19. The difference was statistically significant. PSA density in high grade patients were median 0.70 whereas in other cases 0.21. The difference was statistically significant. For high grade cases, PSA density cut-off values for 0.90, 0.80, and 0.70 sensitivity levels were 0.10, 0.13 and 0.18 respectively. In a previous study, PSA cut-off value was reported 0.13 for 0.90 sensitivity (Zheng, et al., 2008).

In 0-10 range, PSA densities in malignant (median 0.21) and benign patients (median 0.16) were statistically different. This result shows the value of PSA density also in problematic range of PSA.

For high grade carcinoma in cases whose serum PSA level is between 0 and 10, median PSA density was 0.28 whereas corresponding value was 0.17 in other cases. The difference was statistically significant.

Age specific PSA ranges

Age specific features of PSA are also examined. When 0.90 sensitivity level is taken as cut-off value, PSA threshold is 2.5 for fifth and sixth decades, 4 for seventh decade and 6 for eighth decade. The recommended upper reference value for serum PSA (95th percentile) for men were 2.5, 3.5, 4.5, and 6.5 ng/ml for fifth, sixth, seventh and eight decades respectively (Schmid, et al., 2004). When only DRE negative patients have been evaluated, PSA threshold is 5 for fifth and seventh decades, 4 for sixth decade and 6 for eighth decade.

Age specific reference ranges for high grade carcinoma were also examined. At the level of 0.90 sensitivity, PSA cut-off values were 10 for fifth decade and 6 for other decades, a result possibly reflects low incidence of high grade carcinoma in young patients.

Free PSA, fPSA/PSA

Free PSA serum level is available in 1038 patients. In patients lower than 25% fPSA/PSA, malignancy was 29%, while it was 21% in other patients. ROC AUC of fPSA was higher than free/total PSA (0.655 versus 0.599). Additionally, in cases who has less than 25% fPSA/PSA, rate of high grade malignancy was 10.8% whereas in other patients it was 9.2%. The difference was not statistically significant, so the value of fPSA/PSA in differentiating high grade carcinoma is questionable.

A percent-free PSA of greater than 25 percent is 95 percent sensitive in excluding prostate cancers when PSA values are in the ambiguous range of 4 to 10 ng per ml (4 to 10 μg per L). Free PSA serum level was available in 750 patients who had serum PSA level between 0 and 10. The cases whose fPSA/PSA ratio under 25%, 18% was malignant whereas the cases over 25% was 16% malignant. The difference was statistically insignificant. Sensitivity for 25% cut-of value was 0.71 in contrast to reported 0.95 value (Catalona, et al., 1998). The suggested 25% threshold was not predictive in our series. ROC AUC for fPSA was not statistically significant and ROC AUC for free/total PSA (0.560, p=0.031) could not show a powerful predictive value. According to literature, several pre-analytical and clinical factors may influence the free/total PSA ratio, e.g. instability of free PSA both at 4 °C and at room temperature, assay characteristics (equimolar versus skewed response), and a "dilution effect" in large prostates due to concomitant BPH (C. Stephan, et al., 1997).

Free PSA and free/total PSA has shown no statistical significance for prediction of high grade cases in PSA 0-10 range.

Comparison of classical approaches

Summary of ROC AUCs of classical approaches shows that the highest AUC is seen in PSA of 5th decade. However, the number of patients in this group is very low (n=45). AUC of PSA in 8th decade is also high. The AUC ROC curve of PSA density is slightly higher than PSA (0.740 versus 0.720). PSA density seems to be not adding a lot to PSA alone.

When ROC AUCs of classical approaches for high grade malignancy was reviewed, it was seen that the highest ROC AUC was for PSA density.

Dynamic approaches

Dynamic approaches have been studied, namely PSADT and PSA velocity. The recurrent biopsies were not available in all of the patients in the group, 446 of the patients had previous PSA levels but neither dynamic concept revealed a statistically significant relation to malignancy. PSA velocity was median 0.43/year for benign cases and 0.68/year for malignant cases. PSA doubling time was median 2.2 years for benign cases and 1.9 years for malignant cases. The reason of absence of the relation is not easy to explain. Because of low incidence of the malignancy in our country, the benign factors such as BPH or prostatitis may cause elevation of PSA and dominate the picture. Another cause may be inconsistency in laboratory results.

Dynamic concepts were not statistically significant in prediction of high grade carcinoma as in the case of carcinoma. PSA velocity was median 0.46/year for benign and low grade cases and 1.63/year for high grade cases. PSA doubling time was median 2.2 years for benign and low grade cases and 1.0 years for high grade cases (p=0.094). P value for PSADT was not very high, suggesting a relation which can be showed in larger series.

Logistic Regression

We applied three different LR analyses because some patients do not have TRUS and/or fPSA results. The first analysis was performed for the patients who had TRUS results. Age, serum PSA level, serum free PSA level, percent of free/total PSA,

prostate volume, PSA density, DRE result, TRUS result have selected as covariates. Age, free/total PSA, PSA density and DRE were significant variables in this analysis. In a previous Japanese study which does not contain free/total PSA in the analysis has revealed DRE, TRUS, prostate volume as significant variables, a quite different result from our study (Shigemura, et al., 2008).

The second analysis was performed adding the patients who had no TRUS results. Age, serum PSA level, serum free PSA level, percent of free/total PSA, DRE result have selected as covariates. Age, PSA, free/total PSA, DRE were significant variables in this analysis. A similar previous study revealed exactly same variables (Karakiewicz, et al., 2005).

The third analysis was performed adding the patients who had no fPSA levels. Age, serum PSA level, DRE results have selected as covariates. All three of these variables were significant in this analysis as confirmed by a previous study (Karakiewicz, et al., 2005).

ROC AUC's of three LR analyses were 0.755, 0.747, and 0.761 respectively. Previous studies reported 0.69-0.75 ROC AUC's, similar to our results (Eastham, et al., 1999; Garzotto, et al., 2003; Karakiewicz, et al., 2005; Lopez-Corona, et al., 2003). Comparison three LR sets has shown that in spite of high number of patients (over 1000 for each analysis), TRUS results or fPSA have not an important effect on prediction power of the model. Additionally, the first LR analysis shows that presence of abnormality in TRUS has not been selected as a significant variable in LR analysis.

LR analysis was also performed for high grade tumours. For the patients who had TRUS results, age, PSA density and DRE was significant variables. The second analysis was performed adding the patients who had no TRUS results. Age, serum PSA level, percent of free/total PSA, and DRE have been selected as statistically significant variables. The third analysis was performed adding the patients who had no fPSA levels. Age, serum PSA level, DRE were significant variables.

LR analysis of the cases that have PSA between 0-10 showed that, in the first LR set, free/total PSA was could not take place in multivariate model, but age, PSA density, and DRE were significant. In a similar previous study which does not contain free/total PSA in the analysis, age, PSA density, DRE, TRUS were significant variables (Garzotto, et al., 2003). In another study which does not contain free/total PSA in the analysis has revealed only prostate volume as significant variable, a quite different result from our study (Shigemura, et al., 2008). In the second LR analysis, age, PSA and DRE and free/total PSA were significant whereas in the third LR analysis age, PSA and DRE were significant. The ROC AUC's of three LR sets were 0.717, 0.656 and 0.662 respectively. The first LR analysis seems to be most successful, but presence of PSA density in the model limits its practical use because when TRUS is performed, taking prostate biopsy is an easy intervention. The other two sets have very close ROC AUC's, 0.656 and 0.662, which are slightly lower than result of a previous study which was 0.73 (Garzotto, et al., 2003).

Artificial Neural Network

Artificial Neural Network was another method which was applied in this study. The evaluation in study group have revealed good results with an AUC ROC value of 0.746, however in test group, the method has given disappointing results with a AUC ROC curve value of 0.562. This result does not confirm previous literature which reports successful ANN results (Babaian, et al., 2000; Finne, et al., 2000; Remzi, et al., 2003; C. Stephan, et al., 2002). This may be due to defects in our ANN design such as overfitting, or may be due to absence of validation group in some studies (Remzi, et al., 2003). Overfitting is a frequent complication of ANN design. In case of overfitting, the system is adjusted to learn individual cases, rather than producing generalized approach. Further studies with different number of layers and/or neurons and different number of iterations may produce more successful results.

ANN was also applied for prediction of high grade cases. ROC AUC with the system is 0.721. The test group revealed an AUC of 0.709, which is a favourable result compared to use of ANN in prediction of carcinoma.

ANN ROC AUC was 0.644 in the patients whose PSA level was between 0 and 10, however it failed to show a statistically significant performance in test group. In the same group, ANN for high grade cases revealed an AUC ROC of 0.741, but the model was unsuccessful in test group.

Decision Tree Analysis

The decision tree revealed 10 terminal nodes and two of them showed malignancy over 50%, one of them showed 0% malignancy. The test group showed similar results when the decision tree is applied.

Decision tree for high grade carcinoma shows that the number of terminal nodes is five. Two of these nodes had a high grade carcinoma probability over 20, a result confirmed by also in validation group.

This study is the first one applying QUEST decision tree analysis in prediction problem of prostate cancer. In the previous literature, the same problem was investigated by Garzotto et al. who performed CART analysis which has a similar algorithm to QUEST. Their study was performed on 1433 patients, using demographic data, DRE and TRUS results and serum PSA levels (Garzotto, Beer, et al., 2005). Their results were not comparable to our study due to differences in included parameters because their analysis contains TRUS data and does not contain serum free PSA level.

The decision tree which is created in this study seems valuable because it defines two subgroups (nodes) of patients who have a very low probability of being cancer; (a) man who have serum PSA level below 6 ng/mL, DRE negative, and serum free PSA level over 0.81 ng/mL, (b) man who have serum PSA level below 6 ng/mL, DRE negative, serum free PSA level $\leq$ 0.81 ng/mL, and age $\leq$57 years. The model shows 0.99 sensitivity in study group and 0.97 sensitivity in validation group. According to the model, 13% of the patients may be saved from biopsy with a minimal loss in sensitivity. The AUC of the decision tree is slightly higher than free PSA/PSA ratio alone. The model has slightly lower AUC than LR, but it may be accepted as a

significant tool because of its advantage of simplicity for both understanding the model and using it in clinical application.

This model has also revealed an interesting result; the patients with serum PSA levels below 6 ng/mL, negative DRE and low serum free PSA level (<=0.81) were divided into two nodes. Men below 58 years old had a low probability of malignancy (4%) compared to older man (16%) with the same features. It should also be noted that, the decision tree algorithm has preferred fPSA to percent free PSA. Percent free PSA is a derivative of fPSA and a low free PSA shows the tendency to a low percent free PSA. As generally accepted, a low free PSA/PSA ratio is suggestive of prostate cancer, however there has been no well-known effect of age on this relation. The decision tree revealed that low free PSA does not increase probability of malignancy in young patients with serum PSA level below 6 ng/mL and negative DRE. A recent study also reported that percent free PSA was not valuable in prediction of prostate carcinoma in men between 44-50 ages (Vickers, et al., 2007). We would like to note that clinical value of fPSA in different ethnical groups may be variable; in a previous study on Turkish population, percent free PSA was reported as a poor predictor of biopsy outcome (Akduman, et al., 2000).

The findings of the present study suggested that a man with a serum PSA below 6 ng/mL, serum free PSA over 0.81 ng/mL, and negative DRE has a very low probability of prostate cancer. Additionally, if serum PSA level is below 6 mg/dL and DRE is negative in a patient younger than 58 years old, there may be no need for ordering a free PSA level, since it may not be helpful in prediction of prostate cancer. It also seemed possible that free PSA and percent free PSA did not have the same predictive value in different ethnical groups. Further studies are needed to understand the relations of free PSA and free PSA/PSA ratio with age and different ethnical groups. Given that the application of DT analysis revealed unexpected results in the present study, it might be considered as a useful data mining technique with the capacity to give valuable clues in complex medical problems.

Genetic Algorithm

Analysis of the patients who have PSA values between 4-10 by genetic algorithm has produced the following rule: If PSA is over 4.5 and DRE is positive and PSA density over 0.142, the patient is likely to have cancer. Using this criterion, sensitivity is 0.58 and specificity is 0.78 in the data set. ROC AUC is 0.671 (95% CI: 0.604-0.737 p=0.000) by this method. The rule has been also applied to test group.

On the same data set, according to LR, age, PSA density and DRE are significant in the prediction of malignancy with an ROC AUC of 0.718 (95% CI: 0.658-0.778, p=0.000).

The analysis by genetic algorithm has given a simple rule for prediction of malignancy with 0.58 sensitivity 0.78 specificity. ROC AUC is 0.671 by this method. AUC of GA is slightly better than single approaches. The best AUC is obtained by PSA density is 0.654, showing a close performance to GA. Studies in larger samples would help to show if there is a real difference in these approaches. AUC results for GA are slightly lower than the value which was obtained by LR, but it has the advantage of being simple. The result can be summarized as; "If DRE is positive, PSA is over 4.5 and PSA density is over 0.142, biopsy should be seriously considered". In contrast to LR, it does not need complex calculations.

This study is the first study that examines the usefulness of GA in the prediction of prostate cancer. These results are promising, and further studies with larger and/or different patient groups should be considered.

Comparison of complex approaches

Summary of complex approaches as comparison of ROC AUC's have shown that, three LR methods, DT and ANN have very close results, however application of ANN in test group showed a significantly lower AUC, causing to diminish the value of ANN in this problem.

Overall evaluation of methods for prediction of high grade carcinoma has shown that three LR models (AUC ROC curves of 0.839, 0.813, 0.822) and DT (0.818) have very close success. ANN has a smaller AUC ROC (0.721).

On 0-10 range of PSA, LR and DT were still successful, ANN failed in test group.

Three different LR analyses for prediction of high grade cases in PSA 0-10 range revealed very close performance, the largest set giving the classical variables as significant, namely age, PSA and DRE.

Final prediction algorithms

As seen in the results above, prediction characteristics for our country is different from previous literature which is largely studied by developed countries. It is apparent that a tool which supports biopsy decision for Turkish population would be helpful. The prediction algorithms were prepared to produce probability of malignancy and high grade malignancy as percents. Giving the probability of high grade carcinoma would be helpful because the physician may take higher number of core biopsies to prevent false negative biopsy result in case of a substantial high grade carcinoma possibility. The result would give probability, to help the decision of the physician, and some patients would like to know their probability of being cancer. However, when probability is high, biopsy is strongly advisable. So we decided to give the result of "probability is too high" over 50% for malignancy and 20% for high grade malignancy. This approach helped us to exclude some extreme values from logistic regression set, providing more smooth data. As seen in Table 35 and Table 57, the most successful models for the prediction of prostate cancer are LR and DT. We prepared two hybrid models using both of these models, one for cancer, and the other for high grade cancer. First, we have determined the nodes which give very high possibilities and very low possibilities in DTs. After the cases in these nodes were removed, the remaining cases were further analysed by LR. For carcinoma algorithm, any probability over 50% was regarded as "High probability", any probability below 1% was regarded as "Low probability. For high grade carcinoma algorithm, any probability over 20% was regarded as "High probability", any probability below 1% was regarded as "Low probability.

Significant variables in logistic regression analysis of the patients who have been remained after elimination of DT cases (n=1197) were age, PSA and DRE for both malignancy and high grade malignancy.

Although prostate biopsy is required for the diagnosis of prostatic carcinoma, this invasive and expensive procedure should be avoided in men with a low probability of harbouring prostatic carcinoma (C Stephan, Cammann, Meyer, Lein, & Jung, 2007). The model could prevent 33 biopsies from our data set without a loss from sensitivity. The number of patients corresponds to 4.4% of our patients who has PSA level between 0 and 10.

Decision Support Tool

Prostate cancer incidence may vary between countries and a decision support tool of a geographic region may not be effective in another region (Suzuki, et al., 2006). To date, a prediction model for prostate cancer for our country had not been developed. We have developed a model with the help of local data and published a tool designed with the help of this model on the web.

Results of the user questionnaire

It was seen that the urologists who participated in the study are regular users of computers. They use a computer for approximately 16 hours a week, more than two hours a day. There was no relation between user's age and duration of computer use. Younger physicians may have been predicted to use computers more frequently, but in our study, participants were the urologists who voluntarily answered the questionnaire, so a sampling bias may be the cause of this unexpected finding.

The mean ACH of the users was 4.2 in a five graded scale. The users had quite positive attitudes towards use of computers in health care. Total hours of weekly computer use and ACH have shown a positive correlation.

The users have given a mean score of 3.7 to the decision support tool. This score may be evaluated as high, however it is apparently lower than ACH which is mean 4.2. Examination of the eight questions related to the tool, may help to find the

source of the relatively low score. Twelve users have agreed or strongly agreed that "input of the system is not sufficient". The second source of negativity was the presence of eight users who agreed or strongly agreed with the difficulty of finding time to use the tool. The users may be right in their opinion that input of the system is not sufficient. It does not include possible factors such as family history of cancer and body mass index, which were not included in our analysis on prostate cancer patients, because of the retrospective nature of the analysis and absence of some patient data. On the other hand 16% of them expressed their concerns about finding time to use tool. Similar concerns about CDSS have been reported in previous studies (Short, et al., 2004; Sittig, et al., 2006; Wilson, et al., 2007). However, using the tool takes just a few seconds, so we believe that this concern is related more to users' perception of the role of computers in healthcare rather than a time problem. The answer to this question is significantly correlated to ACH, suggesting the importance of attitude to using computers in healthcare in feeling a time problem with using the tool.

Thirty seven (74%) users agreed or strongly agreed on the need for such a tool. Answers to this question have shown also a correlation to ACH. Residents scored this question significantly lower than specialists and academics. They may feel more confident about their decisions because of lack of experience. In the case of continuation of similar findings in future studies, this finding needs to be examined.

Forty four (88%) of the users agreed or strongly agreed to use the tool in case of it is further developed. Six were not sure and no negative response was present. The high agreement rate to this question suggests that a significant majority of the physicians may use a system which is evaluated as "developed" by them. The answer to this question showed positive correlation with ACH but no significant correlation was observed with ADST.

Thirty nine (78%) of the users would share the results with their patients, seven (14%) were not sure and four (8%) of them expressed negative opinion about it. The answer to this question has shown positive correlation with ACH and ADST.

When the users were asked about their frequency of using the system, only one user reported that he would not use the system. The other users claimed that they would use the system, in case of difficulty in biopsy decision (32%), frequently (30%), occasionally (26%) and for every patient (10%). The answer to this question has shown positive correlation with ADST, but no significant correlation observed with ACH.

The results of this study demonstrate two important factors for using the prostate biopsy decision support tool. When the answers were collectively evaluated, it was seen that, ACH shows significant relation to ADST, the need for a decision tool for prostatic biopsy, and the desire to share the results with patients. ACH seems to be the most important factor of positive attitude towards the system. On the other hand, ADST seems also important, because it shows a positive relation to the frequency of using the system and sharing the results with patients. In other words, a factor which is related to the user (attitude to use of computers in healthcare), and another factor which is related to both system and user (attitude to tool) are important motivators to use the online decision support tool in this study. In a previous study, it was suggested that physicians' individual computer skills and their attitudes towards the computer's function in disease management and in decision-making were important factors in implementation of CDSS in clinical practice (Toth-Pal, Wårdh, Strender, & Nilsson, 2008). The attitudes of practitioners are a significant factor in the acceptance and efficiency of use of information technologies in practice (Grant, et al., 2006; Ward, Stevens, Brentnall, & Briddon, 2008). To improve computer use in healthcare, the development of positive attitudes of physicians to use of computers in healthcare may be the key factor. Changes in medical training may help the integration of technology to medical practice (Grant et al. 2006). Medical informatics lectures in medical schools and the integration of topics related to use of information technologies in healthcare to postgraduate and continuous medical education will possibly increase the acceptance of the physicians. As attitude to system is another important factor, informing the users about the logic of the individual system, and

redesigning the system according to user feedback may be helpful to increase acceptance.

Limitations of the study

The patients whom we evaluate are usually symptomatic patients, because screening is not habitual in our country. So the sample does not reflect the real patient profile in the region. Additionally, in a screening study, the sensitivity and specificity of PSA would possibly different from our results. A screening study for Turkish population is needed for more reliable profile. The study is retrospective, so some data cannot be obtained. Body mass index and prostate carcinoma in relatives was shown as important predictors in some studies.

Sample of the study is mainly from Southern-west Anatolia, a randomization in the region is also not available. The results may not be generalizable to all Turkey.

This questionnaire was conducted on a sample of voluntary urologists who were not selected by systematic sampling. The opinions of the volunteers possibly show a bias in favour of the tool, because they may show more interest to use of computers in healthcare. This may limit the possibility of generalizing the results.

CHAPTER 5

CONCLUSIONS

According to multivariate analyses, age, serum PSA level and DRE seems to be most important variables for prediction of prostatic carcinoma in our population. Free PSA, fPSA/PSA, and PSA density have a limited value. In cases under 25% fPSA/PSA, an increased probability in prostatic carcinoma is not observed in our population.

Artificial Neural Network was another method which was applied in this study. In spite of good ROC AUC values, ANN failed to show success in validation group, however ANN was successful for prediction of high grade cases.

This study is the first one applying QUEST decision tree analysis in prediction problem of prostate cancer. The findings of the DT model suggested that a man with a serum PSA below 6 ng/mL, serum free PSA over 0.81 ng/mL, and negative DRE has a very low probability of prostate cancer. Additionally, if serum PSA level is below 6 mg/dL and DRE is negative in a patient younger than 58 years old, there may be no need for ordering a free PSA level, since it may not be helpful in prediction of prostate cancer. It also seemed possible that free PSA and percent free PSA did not have the same predictive value in different ethnical groups. Further studies are needed to understand the relations of free PSA and free PSA/PSA ratio

with age and different ethnical groups. Given that the application of DT analysis revealed unexpected results in the present study, it might be considered as a useful data mining technique with the capacity to give valuable clues in complex medical problems.

AUC results for GA are slightly lower than the value which was obtained by LR, but it has the advantage of being simple. The result can be summarized as; "If DRE is positive, PSA is over 4.5 and PSA density is over 0.142, biopsy should be seriously considered". In contrast to LR, it does not need complex calculations. This study is the first study that examines the usefulness of GA in the prediction of prostate cancer. These results are promising, and further studies with larger and/or different patient groups should be considered.

It was seen that most useful methods for prediction of prostatic carcinoma are LR and DT. Two hybrid models for prediction of probability of carcinoma and high grade carcinoma were designed. These models were used to design a decision support tool which was published on the Web.

This study is the first study extensively evaluating the decision making for the prediction of prostate biopsy in Turkish population. Because the incidence of prostate cancer is low in Turkey, the results of the study may be conflicting with previous studies. Some clues for strategies in low incidence countries may emerge from the study. The results show that, the model for prediction of prostatic carcinoma in a country, or in a geographic region must be designed according to local data and periodic epidemiologic trends related to prostate cancer.

The opinions of the urologists about the web based decision support tool for prostate cancer prediction were influenced by two factors. The first factor was the attitude of the user to computer use in healthcare practice, the other factor is the attitude of the user to the tool. To increase the acceptance, education and training of the physicians about use of information technologies in health, informing the users about the logic

of the system, and redesigning the system according to user feedbacks may be helpful.

REFERENCES

Akduman, B., Alkibay, T., Tuncel, A., & Bozkirli, I. (2000). The value of percent free prostate specific antigen, prostate specific antigen density of the whole prostate and of the transition zone in Turkish men. *Can J Urol, 7*(5), 1104-1109.

Allard, W. J., Zhou, Z., & Yeung, K. K. (1998). Novel immunoassay for the measurement of complexed prostate-specific antigen in serum. *Clin Chem, 44*(6 Pt 1), 1216-1223.

Arai, Y., Maeda, H., Ishitoya, S., Okubo, K., Okada, T., & Aoki, Y. (1997). Prospective evaluation of prostate specific antigen density and systematic biopsy for detecting prostate cancer in Japanese patients with normal rectal examinations and intermediate prostate specific antigen levels. *J Urol, 158*(3 Pt 1), 861-864.

Babaian, R. J., Fritsche, H., Ayala, A., Bhadkamkar, V., Johnston, D. A., Naccarato, W., et al. (2000). Performance of a neural network in detecting prostate cancer in the prostate-specific antigen reflex range of 2.5 to 4.0 ng/mL. *Urology, 56*(6), 1000-1006.

Babaian, R. J., Fritsche, H. A., & Evans, R. B. (1990). Prostate-specific antigen and prostate gland volume: correlation and clinical application. *J Clin Lab Anal, 4*(2), 135-137.

Banerjee, M., Biswas, D., Sakr, W., & Wood, D. P., Jr. (2000). Recursive partitioning for prognostic grouping of patients with clinically localized prostate carcinoma. *Cancer, 89*(2), 404-411.

Benson, M. C., Whang, I. S., Olsson, C. A., McMahon, D. J., & Cooner, W. H. (1992). The use of prostate specific antigen density to enhance the predictive value of intermediate levels of serum prostate specific antigen. *J Urol, 147*(3 Pt 2), 817-821.

Bernal-Delgado, E., Latour-Perez, J., Pradas-Arnal, F., & Gomez-Lopez, L. I. (1998). The association between vasectomy and prostate cancer: a systematic review of the literature. *Fertil Steril, 70*(2), 191-200.

Bindels, R., Hasman, A., Derickx, M., Van Wersch, J., & Winkens, R. (2003). User satisfaction with a real-time automated feedback system for general practitioners: a quantitative and qualitative study. *Int J Qual Health Care, 15*(6), 501-508.

Branche, C. L. (2002). Digital Rectal Examination. *Gale Encyclopedia of Cancer* Retrieved 01.25.2009, 2009, from http://www.healthline.com/galecontent/digital-rectal-examination

Brawer, M. K., Meyer, G. E., Letran, J. L., Bankson, D. D., Morris, D. L., Yeung, K. K., et al. (1998). Measurement of complexed PSA improves specificity for early detection of prostate cancer. *Urology, 52*(3), 372-378.

Cabana, M., Rand, C., Powe, N., Wu, A., Wilson, M., Abboud, P., et al. (1999). Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA, 282*(15), 1458-1465.

Carter, H. B., Pearson, J. D., Metter, E. J., Chan, D. W., Andres, R., Fozard, J. L., et al. (1995). Longitudinal evaluation of serum androgen levels in men with and without prostate cancer. *Prostate, 27*(1), 25-31.

Catalona, W. J., Partin, A. W., Slawin, K. M., Brawer, M. K., Flanigan, R. C., Patel, A., et al. (1998). Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. *JAMA, 279*(19), 1542-1547.

Catalona, W. J., Smith, D. S., Ratliff, T. L., Dodds, K. M., Coplen, D. E., Yuan, J. J., et al. (1991). Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. *N Engl J Med, 324*(17), 1156-1161.

Chun, F., Karakiewicz, P., Briganti, A., Walz, J., Kattan, M., Huland, H., et al. (2007). A critical appraisal of logistic regression-based nomograms, artificial neural networks, classification and regression-tree models, look-up tables and risk-group stratification models for prostate cancer. *BJU Int, 99*(4), 794-800.

Cunha, A. C., Weigle, B., Kiessling, A., Bachmann, M., & Rieber, E. P. (2006). Tissue-specificity of prostate specific antigens: comparative analysis of transcript levels in prostate and non-prostatic tissues. *Cancer Lett, 236*(2), 229-238.

Djavan, B., Remzi, M., Zlotta, A. R., Ravery, V., Hammerer, P., Reissigl, A., et al. (2002). Complexed prostate-specific antigen, complexed prostate-specific antigen density of total and transition zone, complexed/total prostate-specific antigen ratio, free-to-total prostate-specific antigen ratio, density of total and transition zone prostate-specific antigen: results of the prospective multicenter European trial. *Urology, 60*(4 Suppl 1), 4-9.

Eastham, J. A., May, R., Robertson, J. L., Sartor, O., & Kattan, M. W. (1999). Development of a nomogram that predicts the probability of a positive prostate biopsy in men with an abnormal digital rectal examination and a prostate-specific antigen between 0 and 4 ng/mL. *Urology, 54*(4), 709-713.

Ellison, L., Cheli, C. D., Bright, S., Veltri, R. W., & Partin, A. W. (2002). Cost-benefit analysis of total, free/total, and complexed prostate-specific antigen for prostate cancer screening. *Urology, 60*(4 Suppl 1), 42-46.

Epperly, T., & Moore, K. (2000). Health issues in men: part I: Common genitourinary disorders. *Am Fam Physician, 61*(12), 3657-3664.

Fidaner, C., Eser, S. Y., & Parkin, D. M. (2001). Incidence in Izmir in 1993-1994: first results from Izmir Cancer Registry. *Eur J Cancer, 37*(1), 83-92.

Filella, X., Alcover, J., Molina, R., Corral, J. M., Carretero, P., & Ballesta, A. M. (2000). Measurement of complexed PSA in the differential diagnosis between prostate cancer and benign prostate hyperplasia. *Prostate, 42*(3), 181-185.

Finne, P., Finne, R., Auvinen, A., Juusela, H., Aro, J., Maattanen, L., et al. (2000). Predicting the outcome of prostate biopsy in screen-positive men by a multilayer perceptron network. *Urology, 56*(3), 418-422.

Foti, A. G., Cooper, J. F., Herschman, H., & Malvaez, R. R. (1977). Detection of prostatic cancer by solid-phase radioimmunoassay of serum prostatic acid phosphatase. *N Engl J Med, 297*(25), 1357-1361.

Garg, A., Adhikari, N., McDonald, H., Rosas-Arellano, M., Devereaux, P., Beyene, J., et al. (2005). Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. *JAMA, 293*(10), 1223-1238.

Garzotto, M., Beer, T. M., Hudson, R. G., Peters, L., Hsieh, Y. C., Barrera, E., et al. (2005). Improved detection of prostate cancer using classification and regression tree analysis. *J Clin Oncol, 23*(19), 4322-4329.

Garzotto, M., Hudson, R. G., Peters, L., Hsieh, Y. C., Barrera, E., Mori, M., et al. (2003). Predictive modeling for the presence of prostate carcinoma using clinical, laboratory, and ultrasound parameters in patients with prostate specific antigen levels. *Cancer, 98*(7), 1417-1422.

Garzotto, M., Park, Y., Mongoue-Tchokote, S., Bledsoe, J., Peters, L., Blank, B. H., et al. (2005). Recursive partitioning for risk stratification in men undergoing repeat prostate biopsies. *Cancer, 104*(9), 1911-1917.

Goldberg, D. E. (1989). *Genetic algorithms in search, optimization, and machine learning* (Repr. with corrections. ed.). Reading, Mass.: Addison-Wesley Pub. Co.

Grant, R., Campbell, E., Gruen, R., Ferris, T., & Blumenthal, D. (2006). Prevalence of basic information technology use by U.S. physicians. *J Gen Intern Med, 21*(11), 1150-1155.

Gretzer, M. B., Epstein, J. I., Pound, C. R., Walsh, P. C., & Partin, A. W. (2002). Substratification of stage T1C prostate cancer based on the probability of biochemical recurrence. *Urology, 60*(6), 1034-1039.

Group, D. E. (2000). Globocan 2000 (Version 1.0). Lyon: International Agency for Research on Cancer.

Grubb, R., Roehl, K., Antenor, J., & Catalona, W. (2005). Results of compliance with prostate cancer screening guidelines. *J Urol, 174*(2), 668-672; discussion 672.

Guinan, P., Bhatti, R., & Ray, P. (1987). An evaluation of prostate specific antigen in prostatic cancer. *J Urol, 137*(4), 686-689.

Gülkesen, K. H., Kılıç, S., Özbilim, G., Gelen, M. T., Danışman, A., & Sargın, C. F. (1999). Use of prostate specific antigen immunohistochemistry in differential diagnosis of prostatic carcinoma; Is it reliable? *Wirchows Arch, 435*, 269.

Hara, M., Koyanagi, Y., Inoue, T., & Fukuyama, T. (1971). [Some physico-chemical characteristics of " -seminoprotein", an antigenic component specific for human seminal plasma. Forensic immunological study of body fluids and secretion. VII]. *Nihon Hoigaku Zasshi, 25*(4), 322-324.

Hayward, R., El-Hajj, M., Voth, T., & Deis, K. (2006). Patterns of use of decision support tools by clinicians. *AMIA Annu Symp Proc*, 329-333.

Hernandez, J., & Thompson, I. M. (2004). Prostate-specific antigen: a review of the validation of the most commonly used cancer biomarker. *Cancer, 101*(5), 894-904.

Horninger, W., Cheli, C. D., Babaian, R. J., Fritsche, H. A., Lepor, H., Taneja, S. S., et al. (2002). Complexed prostate-specific antigen for early detection of prostate cancer in men with serum prostate-specific antigen levels of 2 to 4 nanograms per milliliter. *Urology, 60*(4 Suppl 1), 31-35.

Huber, P. R., Schmid, H. P., Mattarelli, G., Strittmatter, B., van Steenbrugge, G. J., & Maurer, A. (1995). Serum free prostate specific antigen: isoenzymes in benign hyperplasia and cancer of the prostate. *Prostate, 27*(4), 212-219.

Humphrey, P. A. (2004). Gleason grading and prognostic factors in carcinoma of the prostate. *Mod Pathol, 17*(3), 292-306.

Ingelfinger, J. A. (1983). *Biostatistics in clinical medicine*. New York: Macmillan.

Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J., Murray, T., et al. Cancer statistics, 2008. *CA Cancer J Clin, 58*(2), 71-96.

Kalish, J., Cooner, W. H., & Graham, S. D., Jr. (1994). Serum PSA adjusted for volume of transition zone (PSAT) is more accurate than PSA adjusted for total gland volume (PSAD) in detecting adenocarcinoma of the prostate. *Urology, 43*(5), 601-606.

Karakiewicz, P. I., Benayoun, S., Kattan, M. W., Perrotte, P., Valiquette, L., Scardino, P. T., et al. (2005). Development and validation of a nomogram predicting the outcome of prostate biopsy based on patient age, digital rectal examination and serum prostate specific antigen. *J Urol, 173*(6), 1930-1934.

Kawakami, S., Numao, N., Okubo, Y., Koga, F., Yamamoto, S., Saito, K., et al. (2008). Development, validation, and head-to-head comparison of logistic regression-based nomograms and artificial neural network models predicting prostate cancer on initial extended biopsy. *Eur Urol, 54*(3), 601-611.

Kälkner, K., Kubicek, G., Nilsson, J., Lundell, M., Levitt, S., & Nilsson, S. (2006). Prostate volume determination: differential volume measurements comparing CT and TRUS. *Radiother Oncol, 81*(2), 179-183.

Labrie, F., Dupont, A., Suburu, R., Cusan, L., Tremblay, M., Gomez, J. L., et al. (1992). Serum prostate specific antigen as pre-screening test for prostate cancer. *J Urol, 147*(3 Pt 2), 846-851; discussion 851-842.

Lein, M., Jung, K., Elgeti, U., Petras, T., Stephan, C., Brux, B., et al. (2001). Comparison of the clinical validity of free prostate-specific antigen, alpha-1 antichymotrypsin-bound prostate-specific antigen and complexed prostate-specific antigen in prostate cancer diagnosis. *Eur Urol, 39*(1), 57-64.

Loh, W., & Shih, Y. (1997). Split selection methods for classification trees. *STATISTICA SINICA, 7*(4), 815-840.

Lopez-Corona, E., Ohori, M., Scardino, P. T., Reuter, V. E., Gonen, M., & Kattan, M. W. (2003). A nomogram for predicting a positive repeat prostate biopsy in patients with a previous negative biopsy session. *J Urol, 170*(4 Pt 1), 1184-1188; discussion 1188.

Matsui, Y., Utsunomiya, N., Ichioka, K., Ueda, N., Yoshimura, K., Terai, A., et al. (2004). The use of artificial neural network analysis to improve the predictive accuracy of prostate biopsy in the Japanese population. *Jpn J Clin Oncol, 34*(10), 602-607.

Mehik, A. (2001). Epidemiological and diagnostical aspects of prostatitis. *Basic anatomy, histology and physiology related to the prostate gland* Retrieved 01.24, 2009, from http://herkules.oulu.fi/isbn9514265068/html/x149.html

Mistry, K., & Cable, G. Meta-analysis of prostate-specific antigen and digital rectal examination as screening tests for prostate carcinoma. *J Am Board Fam Pract, 16*(2), 95-101.

Mora, L., Buettner, R., Ahmad, N., Bassel, Y., Jove, R., & Seigne, J. Prostate adenocarcinoma: cellular and molecular abnormalities. *Cancer Control, 8*(6), 551-561.

Muezzinoglu, T., Lekili, M., Eser, E., Uyanik, B. S., & Buyuksu, C. (2005). Population standards of prostate specific antigen values in men over 40: community based study in Turkey. *Int Urol Nephrol, 37*(2), 299-304.

Naitoh, J., Zeiner, R. L., & Dekernion, J. B. (1998). Diagnosis and treatment of prostate cancer. *Am Fam Physician, 57*(7), 1531-1539, 1541-1532, 1545-1537.

Nam, R. K., Toi, A., Trachtenberg, J., Klotz, L. H., Jewett, M. A., Emami, M., et al. (2006). Making sense of prostate specific antigen: improving its predictive value in patients undergoing prostate biopsy. *J Urol, 175*(2), 489-494.

Oesterling, J. E., Jacobsen, S. J., Chute, C. G., Guess, H. A., Girman, C. J., Panser, L. A., et al. (1993). Serum prostate-specific antigen in a community-based

population of healthy men. Establishment of age-specific reference ranges. *JAMA, 270*(7), 860-864.

Parekh, D., Ankerst, D., Higgins, B., Hernandez, J., Canby-Hagino, E., Brand, T., et al. (2006). External validation of the Prostate Cancer Prevention Trial risk calculator in a screened population. *Urology, 68*(6), 1152-1155.

Park, S., Shinohara, K., Grossfeld, G., & Carroll, P. (2001). Prostate cancer detection in men with prior high grade prostatic intraepithelial neoplasia or atypical prostate biopsy. *J Urol, 165*(5), 1409-1414.

Porter, C. R., Gamito, E. J., Crawford, E. D., Bartsch, G., Presti, J. C., Jr., Tewari, A., et al. (2005). Model to predict prostate biopsy outcome in large screening population with independent validation in referral setting. *Urology, 65*(5), 937-941.

Recker, F., Kwiatkowski, M. K., Huber, A., Stamm, B., Lehmann, K., & Tscholl, R. (2001). Prospective detection of clinically relevant prostate cancer in the prostate specific antigen range 1 to 3 ng./ml. combined with free-to-total ratio 20% or less: the Aarau experience. *J Urol, 166*(3), 851-855.

Remzi, M., Anagnostou, T., Ravery, V., Zlotta, A., Stephan, C., Marberger, M., et al. (2003). An artificial neural network to predict the outcome of repeat prostate biopsies. *Urology, 62*(3), 456-460.

Richardson, T. D., & Oesterling, J. E. (1997). Age-specific reference ranges for serum prostate-specific antigen. *Urol Clin North Am, 24*(2), 339-351.

Riegman, P. H., Vlietstra, R. J., Klaassen, P., van der Korput, J. A., Geurts van Kessel, A., Romijn, J. C., et al. (1989). The prostate-specific antigen gene and the human glandular kallikrein-1 gene are tandemly located on chromosome 19. *FEBS Lett, 247*(1), 123-126.

Rittenhouse, H. G., & Chan, D. W. (1999). Can complexed PSA be used as a single test for detecting prostate cancer? *Urology, 54*(1), 4-5.

Roscigno, M., Scattoni, V., Bertini, R., Pasta, A., Montorsi, F., & Rigatti, P. (2004). Diagnosis of prostate cancer. State of the art. *Minerva Urol Nefrol, 56*(2), 123-145.

Sakr, W., Grignon, D., Crissman, J., Heilbrun, L., Cassin, B., Pontes, J., et al. (1994). High grade prostatic intraepithelial neoplasia (HGPIN) and prostatic adenocarcinoma between the ages of 20-69: an autopsy study of 249 cases. *In Vivo, 8*(3), 439-443.

Sakr, W., & Partin, A. (2001). Histological markers of risk and the role of high-grade prostatic intraepithelial neoplasia. *Urology, 57*(4 Suppl 1), 115-120.

Schacht, M. J., Garnett, J. E., & Grayhack, J. T. (1984). Biochemical markers in prostatic cancer. *Urol Clin North Am, 11*(2), 253-267.

Schmid, H. P., McNeal, J. E., & Stamey, T. A. (1993). Observations on the doubling time of prostate cancer. The use of serial prostate-specific antigen in patients with untreated disease as a measure of increasing cancer volume. *Cancer, 71*(6), 2031-2040.

Schmid, H. P., Riesen, W., & Prikler, L. (2004). Update on screening for prostate cancer with prostate-specific antigen. *Crit Rev Oncol Hematol, 50*(1), 71-78.

Semjonow, A., De Angelis, G., Oberpenning, F., Schmid, H. P., Brandt, B., & Hertle, L. (2000). The clinical impact of different assays for prostate specific antigen. *BJU Int, 86*(5), 590-597.

Shariat, S., Margulis, V., Lotan, Y., Montorsi, F., & Karakiewicz, P. (2008). Nomograms for bladder cancer. *Eur Urol, 54*(1), 41-53.

Shigemura, K., Arakawa, S., Yamanaka, K., Yasui, N., Matsubara, S., Iwamoto, T., et al. (2008). Potential predictive factors of positive prostate biopsy in the Japanese population. *Int Urol Nephrol, 40*(1), 91-96.

Shipley, W. U., Thames, H. D., Sandler, H. M., Hanks, G. E., Zietman, A. L., Perez, C. A., et al. (1999). Radiation therapy for clinically localized prostate cancer: a multi-institutional pooled analysis. *JAMA, 281*(17), 1598-1604.

Short, D., Frischer, M., & Bashford, J. (2004). Barriers to the adoption of computerised decision support systems in general practice consultations: a qualitative study of GPs' perspectives. *Int J Med Inform, 73*(4), 357-362.

Shortliffe, E., Axline, S., Buchanan, B., Merigan, T., & Cohen, S. (1973). An artificial intelligence program to advise physicians regarding antimicrobial therapy. *Comput Biomed Res, 6*(6), 544-560.

Sittig, D., Krall, M., Dykstra, R., Russell, A., & Chin, H. (2006). A survey of factors affecting clinician acceptance of clinical decision support. *BMC Med Inform Decis Mak, 6*, 6.

Snow, P. B., Smith, D. S., & Catalona, W. J. (1994). Artificial neural networks in the diagnosis and prognosis of prostate cancer: a pilot study. *J Urol, 152*(5 Pt 2), 1923-1926.

Song, J., Kim, C., Chung, H., & Kane, R. (2005). Prostate-specific antigen, digital rectal examination and transrectal ultrasonography: A meta-analysis for this diagnostic triad of prostate cancer in symptomatic Korean men. *YONSEI MEDICAL JOURNAL, 46*(3), 414-424.

Spurgeon, S. E., Hsieh, Y. C., Rivadinera, A., Beer, T. M., Mori, M., & Garzotto, M. (2006). Classification and regression tree analysis for the prediction of aggressive prostate cancer on biopsy. *J Urol, 175*(3 Pt 1), 918-922.

Stamey, T. A. (2004). The era of serum prostate specific antigen as a marker for biopsy of the prostate and detecting prostate cancer is now over in the USA. *BJU Int, 94*(7), 963-964.

Stamey, T. A., Johnstone, I. M., McNeal, J. E., Lu, A. Y., & Yemoto, C. M. (2002). Preoperative serum prostate specific antigen levels between 2 and 22 ng./ml. correlate poorly with post-radical prostatectomy cancer morphology: prostate specific antigen cure rates appear constant between 2 and 9 ng./ml. *J Urol, 167*(1), 103-111.

Stamey, T. A., Yang, N., Hay, A. R., McNeal, J. E., Freiha, F. S., & Redwine, E. (1987). Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med, 317*(15), 909-916.

Stephan, C., Cammann, H., Meyer, H., Lein, M., & Jung, K. (2007). PSA and new biomarkers within multivariate models to improve early detection of prostate cancer. *Cancer Lett, 249*(1), 18-29.

Stephan, C., Cammann, H., Semjonow, A., Diamandis, E. P., Wymenga, L. F., Lein, M., et al. (2002). Multicenter evaluation of an artificial neural network to increase the prostate cancer detection rate and reduce unnecessary biopsies. *Clin Chem, 48*(8), 1279-1287.

Stephan, C., Lein, M., Jung, K., Schnorr, D., & Loening, S. A. (1997). The influence of prostate volume on the ratio of free to total prostate specific antigen in serum of patients with prostate carcinoma and benign prostate hyperplasia. *Cancer, 79*(1), 104-109.

Suzuki, H., Komiya, A., Kamiya, N., Imamoto, T., Kawamura, K., Miura, J., et al. (2006). Development of a nomogram to predict probability of positive initial prostate biopsy among Japanese patients. *Urology, 67*(1), 131-136.

Thompson, I., & Ankerst, D. (2007). Prostate-specific antigen in the early detection of prostate cancer. *CMAJ, 176*(13), 1853-1858.

Toth-Pal, E., Wårdh, I., Strender, L., & Nilsson, G. (2008). Implementing a clinical decision-support system in practice: a qualitative analysis of influencing attitudes and characteristics among general practitioners. *Inform Health Soc Care, 33*(1), 39-54.

Tricoli, J., Schoenfeldt, M., & Conley, B. (2004). Detection of prostate cancer and predicting progression: current and future diagnostic markers. *Clin Cancer Res, 10*(12 Pt 1), 3943-3953.

TUİK, T. İ. K. (2007). İl, yaş grubu ve cinsiyete göre nüfus, 31.12.2007 Retrieved 01.25.2009, 2009, from http://www.tuik.gov.tr/PreIstatistikTablo.do?istab_id=945

Veneziano, S., Pavlica, P., Querze, R., Nanni, G., Lalanne, M. G., & Vecchi, F. (1990). Correlation between prostate-specific antigen and prostate volume, evaluated by transrectal ultrasonography: usefulness in diagnosis of prostate cancer. *Eur Urol, 18*(2), 112-116.

Vickers, A., Ulmert, D., Serio, A., Björk, T., Scardino, P., Eastham, J., et al. (2007). The predictive value of prostate cancer biomarkers depends on age and time to diagnosis: towards a biologically-based screening strategy. *Int J Cancer, 121*(10), 2212-2217.

Wang, T. Y., & Kawaguchi, T. P. (1986). Preliminary evaluation of measurement of serum prostate-specific antigen level in detection of prostate cancer. *Ann Clin Lab Sci, 16*(6), 461-466.

Ward, R., Stevens, C., Brentnall, P., & Briddon, J. (2008). The attitudes of health care staff to information technology: a comprehensive review of the research literature. *Health Info Libr J, 25*(2), 81-97.

Williams, S. G., Millar, J. L., Dally, M. J., Sia, S., Miles, W., & Duchesne, G. M. (2004). What defines intermediate-risk prostate cancer? Variability in published prognostic models. *Int J Radiat Oncol Biol Phys, 58*(1), 11-18.

Wilson, A., Duszynski, A., Turnbull, D., & Beilby, J. (2007). Investigating patients' and general practitioners' views of computerised decision support software for the assessment and management of cardiovascular risk. *Inform Prim Care, 15*(1), 33-44.

Zheng, X., Xie, L., Wang, Y., Ding, W., Yang, K., Shen, H., et al. (2008). The use of prostate specific antigen (PSA) density in detecting prostate cancer in Chinese men with PSA levels of 4-10 ng/mL. *J Cancer Res Clin Oncol, 134*(11), 1207-1210.

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High School	Tevfik Sırrı Gür High School, Mersin	1983

WORK EXPERIENCE

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2005- Present	Akdeniz University, Dpt. of Biostatistics and Medical Informatics	Assistant Professor
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2001-2002	Akdeniz University, Dpt. of Biostatistics and Medical Informatics	Research Assistant
2000-2001	Akdeniz University, Dpt. of Pathology	Specialist
1995-2000	Akdeniz University, Dpt. of Pathology	Research Assistant
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FOREIGN LANGUAGES

Advanced English, Basic German, Basic Japanese

SELECTED PUBLICATIONS

SCI Indexed

1. Uckun-Kitapci A, Haqq AM, Purnell JQ, Newcomb K, Gulkesen H, Underwood LE. Serum ghrelin concentrations are increased in children with growth hormone insensitivity and decrease during long-term insulinlike growth factor-I treatment. J Investig Med. 2008; 56: 26-31.

2. Isken T, Ozgentas HE, Gulkesen KH, Ciftcioglu A. A random-pattern skin-flap model in streptozotocin diabetic rats. Ann Plast Surg. 2006; 57: 323-9.

3. Garipagaoglu M, Tuncel N, Dalmaz MG, Gulkesen H, Toy A, Kizildag AU, Koseoglu FG. Changes in applicator positions and dose distribution between high dose rate brachytherapy fractions in cervix carcinoma patients receiving definitive radiotherapy. Br J Radiol. 2006; 79: 504-9.

4. Frede T, Erdogru T, Zukosky D, Gulkesen H, Teber D, Rassweiler J. Comparison of training modalities for performing laparoscopic radical prostatectomy: experience with 1,000 patients. J Urol. 2005 Aug;174(2):673-8.

5. Kuru O, Senturk UK, Gulkesen H, Demir N, Gunduz F. Physical training increases renal injury in rats with chronic NOS inhibition. Ren Fail. 2005;27(4):459-63.

6. Sezer C, Koksal IT, Usta MF, Gulkesen KH, Erdogru T, Ciftcioglu A, Baykara M. Relationship between mast cell and iNOS expression in testicular tissue associated with infertility. Arch Androl. 2005; 51: 149-58.

7. Bozcuk H, Bilge U, Koyuncu E, Gulkesen H. An application of Genetic Algorithm in conjunction with other data mining methods for estimating outcome after hospitalization in cancer patients. Med Sci Monit. 2004; 10: 246-251.

8. Koksal IT, Dirice E, Yasar D, Sanlioglu AD, Ciftcioglu A, Gulkesen KH, Ozes NO, Baykara M, Luleci G, Sanlioglu S. The assessment of PTEN tumor suppressor gene in combination with Gleason scoring and serum PSA to evaluate progression of prostate carcinoma. Urol Oncol 2004; 22: 307-12.

9. Garipagaoglu M, Kayikcioglu F, Kose MF, Adli M, Gulkesen KH, Kocak Z, Tulunay G. Adding concurrent low dose continuous infusion of cisplatin to radiotherapy in locally advanced cervical carcinoma: a prospective randomized pilot study. Br J Radiol 2004; 77: 581-7.

10. Usta MF, Bivalacqua TJ, Tokatli Z, Rivera F, Gulkesen KH, Sikka SC, Hellstrom WJ. Stratification of penile vascular pathologies in patients with Peyronie's disease and in men with erectile dysfunction according to age: a comparative study. J Urol. 2004; 172: 259-62.

11. Sargin CF, Berker-Karauzum S, Manguoglu E, Erdogru T, Karaveli S, Gulkesen KH, Baykara M, Luleci G. AZF microdeletions on the Y chromosome of infertile men from Turkey. Ann Genet. 2004; 47: 61-8.

12. Garipagaoglu M, Tuncel N, Koseoglu FG, Gulkesen H, Kizildag AU, Toy A, Dalmaz MG. Geometric and dosimetric variations of ICRU bladder and rectum reference points in vaginal cuff brachytherapy using ovoids. Int J Radiat Oncol Biol Phys. 2004; 58: 1607-15.

13. Koksal IT, Erdogru T, Gulkesen H, Sezer C, Usta M, Ciftcioglu A, Baykara M. The potential role of inducible nitric oxide synthase (iNOS) activity in the testicular dysfunction associated with varicocele: an experimental study. Int Urol Nephrol 2004; 36: 67-72.

14. Koksal IT, Usta MF, Akkoyunlu G, Toptas B, Gulkesen KH, Erdogru T, Tuncer M, Baykal A, Ersoy F, Demir R, Baykara M. The potential role of advanced glycation end product and iNOS in chronic renal failure-related testicular dysfunction. An experimental study. Am J Nephrol 2003; 23: 361-8.

15. Baykara M, Erdogru T, Gulkesen KH, Sargin CF, Savas M, Ates M. Does interstitial cystitis urine include possible factors effecting the nociceptive system of the spinal cord? Urol Int 2003; 71: 66-72.

16. Cilli A, Kara A, Ozdemir T, Ogus C, Gulkesen KH. Effects of oral montelukast on airway function in acute asthma. Respir Med 2003; 97: 533-6

Other International Journals

1. Gulkesen KH, Akan H, Akova M, Calikoglu T. Log Analysis of a Turkish Web Portal; Febrile Neutropenia. Stud Health Technol Inform. 2005;116:873-878.

Book Chapter

Bozkurt S, Zayim N, Gülkesen KH, Samur MK. Web Based Personal Nutrition Management Tool. Electronic Healthcare. In: Weerasinghe D, editor. Electronic Healthcare First International Conference, eHealth 2008, London, UK, September 8-9, 2008. Revised Selected Papers. Berlin: Springer; 2009. p. 161-166.

National Journals

1. Gülkesen KH, Özbilim G, Karaveli S. Use of internet in pathology. Turk Bull Pathol, 1999; 16: 52-54.

Full Text Proceedings of International Meetings

1. Gülkesen KH, Köksal IT, Özdem S, Saka O. Prediction of prostate cancer using decision tree analysis. 7th International Congress of Informatics in Health, 9-13 February 2009, Havana, Cuba.

2. Bozkurt S, Gülkesen KH, Zayim N, Aktaş A. Web based patient education on nutrition. 5th International Conference on Information Communication Technologies in Health, 5-7 July 2007, Samos, Greece. 192-197.

3. İşleyen F, Gülkesen KH, Aktaş A. A health related content analysis of spam e-mails. 5th International Conference on Information Communication Technologies in Health, 5-7 July 2007, Samos, Greece. 354-358.

4. Saka O, Zayim N, Gülkesen H. A review of health informatics and eHealth efforts in Turkey. 5th International Conference on Information Communication Technologies in Health, 5-7 July 2007, Samos, Greece. 57-59.

5. Sumen E, Zayim N, Gülkesen KH. Physicians' adoption and satisfaction of laboratory information system. 5th International Conference on Information Communication Technologies in Health, 5-7 July 2007, Samos, Greece. 264-268.

6. Gülkesen KH, Bilge U, Köksal İT, Saka O. Use of genetic algorithm for prediction of prostate cancer. International Symposium on Health Informatics and Bioinformatics, Turkey '07, April 30-May 2, Antalya,

7. Saka O, Zayim N, Gülkesen KH. Medical Informatics Education in Turkey. Medical Informatics 2006, Maastricht, Netherlands. European Notes in Medical Informatics, 2006; 2: 112-117

8. Işleyen F, Gülkesen KH, Zayim N. Readability Of Health Information On Turkish Web Sites. Medical Informatics 2006, Maastricht, Netherlands. European Notes in Medical Informatics, 2006; 2: 409-414.

9. Bozkurt S, Gülkesen KH, Yardımsever M, Özbek F, Saka O. Usage Statistics of a Hospital Web Site; On-line Test Results and Information Service for Patients. Medical Informatics 2006, Maastricht, Netherlands. European Notes in Medical Informatics, 2006; 2: 421-426

10. Gülkesen KH, Beyan T, Gül H, Bıçakçı K. Reliability of Health Information on the Turkish Web Sites; Fever in Children at Home. Medical Informatics 2006, Maastricht, Netherlands. European Notes in Medical Informatics, 2006; 2: 433-438

11. Saka O, Gülkesen KH, Gülden B, Koçgil OD. Evaluation of two search methods in PubMed; the Regular Search and Search by MeSH Terms. MIE 2005, European Notes in Medical Informatics 2005; 1: 1293-1298.

12. Gulkesen KH, Oztas M, Calikoglu E, Baz K, Birol A, Onder M, Calikoglu T, Kitapci MT. Reliability of dermatologic teleconsultations with a web-based technology. MIST 2002, October 3-6, Taipei, Taiwan. Proc MIST 2002, 14-17.

13. Gulkesen KH, Yardimsever M, Saka O, Savas B. Use of Hospital Information System as the source of cancer registry data. MIST 2002, October 3-6, Taipei, Taiwan. Proc MIST 2002, 148-150.

14. Ozkaya MS, Yardimsever M, Gulkesen KH, Tosun O. Linking and embedding "SPSS" to Akdeniz University Hospital Information System. HEALTHCOM 2002, June 6-7, Nancy, France. Proc 4th Int Workshop Enterprise Networking and Comp Healthcare Industry, 132-137.

15. Özkaya MS, Yardımsever M, Gülkesen KH. Akdeniz University Hospital Information System. HEALTHCOM 2001, June 29-July 1, L'Aquila, Italy. Proc 3rd Int Workshop Enterprise Networking and Comp Healthcare Industry, 175-178.

AWARDS

1. Distinguished Service Award, Turkish Medical Informatics Association, 2005.
2. Best Presentation Award, Gülkesen KH, Köksal İT, Özdem S, Saka O. Karar Ağacı Analizi ile Prostat Kanserinin Öngörülmesi. 5th National Medical Informatics Congress, 2008.

HOBBIES

Tennis, Latin Dances, Fishing, Cooking, History of food, Photography