Clinically significant and non significant prostate cancer an ongoing question

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One of the most important problems in urological practice is how to differentiate clinically significant and non significant prostate cancer (Pca) i.e. how to avoid over treatment of tumors with low malignant potential in one hand, and inappropriate less aggressive treatment of significant tumors, on the other hand. At the first place, one should estimate precise local clinical stage and the grade of the disease. Transrectal ultrasound – guided prostate biopsy is the golden standard, but there are few dilemmas concerning prostate biopsy: the number of biopsy cores, inter and intra-observer variations in the grading, the significance of PIN, multifocal character of Pca etc. Our opinion is that sextant or octan biopsy is quite sufficient for the exact detection of clinically insignificant cancers. An additional problem is the discrepancy in grade between biopsy and radical prostatectomy specimen.

Second, the treatment should not be the same for every patient and it is guided by the age and general condition of the patient. The aggressive treatment is recommendable for younger patients, younger than 70-72 years, even for tiny area of cancer in one of the biopsy samples. On the other hand, it is an ethical question, should we insist on detection of small cancer foci at older patients, and make them anxious and unhappy in their last years of life.

Key words Significant prostate cancer, prostate biopsy, number of biopsy cores, treatment options, patient age, radical prostatectomy.

INTRODUCTION

In the last 25 years we have learned a lot about prostate cancer. In the framework of this enhanced knowledge, one of the most important points is that there are clinically significant and not significant types of the disease. This is generally accepted, no one doubts that. For the practicing Urologist the problem is present when all indications are in favour for an organ confined case. In such cases there are no evident signs to confirm which case is significant and which is not. This can lead to overtreatment. Nevertheless, there is a trend to treat tumors that are thought to be small and well differentiated less aggressively. These trends can prove very dangerous because of biopsy sampling error1.

Prostate biopsy is the gold standard for diagnosing prostate cancer. The purpose of histopathological grading of prostate cancer from a needle biopsy is to put the diagnosis and predict the course of the disease of an individual patient, in order to select the most appropriate therapy.

In view of the increasing use of transrectal ultrasound of the prostate, it is likely that a greater number of small, early adenocarcinomas will be diagnosed by needle biopsy. Because of the general correlation between tumor volume and grade, a number of these small lesions will be low grade.2 Therefore, concern has been voiced that detection of small low grade lesions in biopsy may lead to overtreatment of tumors that have low biologic malignant potential.

The question is how much information biopsy can provide to the practicing Urologists regarding the significance of the detected cancer, in order to proceed to an adequate therapy?

One of the stronger predictors of the clinical course of a prostate cancer is the Gleason score. Generally, the practicing Urologist is reluctant to advise a radical procedure to a patient with a low Gleason score prostate cancer. But how accurate is the Gleason score from a small tissue specimen of a biopsy? Is the pathological report from a biopsy representing the real grade of the cancer since, as is generally accepted, the prostate cancer is multifocal and the grade changes between different foci? In addition one has to consider the interference of the human factor in the estimation of the specimen. It is believed that the inter and intra observer variation in the grading of prostate needle biopsies could account for a large part of the fre-
quently reported low Gleason grading.\textsuperscript{3} It has been suggested that the more tissue available for analysis from needle biopsy, the more accurate the cancer grading. Eight biopsies seem to be the optimal number of biopsies. The number of biopsies in a separate session is limited.

An important question arises with the prevalence of small, latent, non-aggressive prostate cancers. Should we try to detect every prostate cancer that is present, for most cancers that would be detected would not require any form of treatment\textsuperscript{1}.

The performance of systematic sextant or octant biopsies must therefore be viewed as an attempt to detect as many clinically significant prostate cancers without detecting too many cancers that could possibly be clinically insignificant.

To predict extracapsular extension and seminal vesicle invasion, the PSA serum level, the Gleason score and the percentage cancer in the biopsy could be useful.

A universal problem is the discrepancy in grade between the biopsy and the radical prostatectomy specimen. This may be due to several factors:

First, there is a tendency to underestimate limited amounts of intermediate grade tumor on needle biopsy\textsuperscript{4}.

The second reason is that, as it is mentioned before, prostate cancer is multifocal and higher grade tumor may be present elsewhere within the gland.

The third factor is the heterogeneity of the grade within the tumor nodule sampled by needle biopsy.\textsuperscript{5}

The practicing Urologist can have valuable information about the significance of a cancer from systematic sextant biopsies, because it has been observed that cancers close to the prostate apex are more likely to extend to the margin and basal cancers easily spread to seminal vesicle and lymph nodes.

Another parameter which is under discussion is the presence of high grade PIN in the tissue specimen without the presence of malignancy. High grade PIN does not necessarily mean that prostate carcinoma is concomitantly present. Major concern exists that prostate carcinoma might not be detected in prostate biopsy specimens with PIN, due to sampling limitations.

Can the presence of PIN be predictive of a later finding aggressive prostate cancer? High grade PIN is most likely a precursor of prostate cancer but since the natural course of prostate cancer is generally slow and the rate of progression from the intraepithelial stage to invasion is highly variable, we doubt whether the presence of PIN can be an indication showing that we should expect a significant prostate cancer in the near future.

Serum prostate specific antigen levels and clinical stage failed to distinguish those cases which could be considered as clinically significant and need aggressive treatment.

New parameters have been used to generate an objective prognosticator that is applicable to individual patients and determine whether the tumor is organ confined and therefore significant. Unfortunately it has proven difficult to find relevant prognostic tissue markers that add significantly to the prognostic value of histopathological grading of needle biopsies. More than 30 markers have been considered to have prognostic value but it has been proved that they are of little value or just promising.\textsuperscript{3}

It seems that perineural tumor invasion, nuclear shape index and microvascular density are of little additional value\textsuperscript{5}.

Some of the more promising markers are:

- The invasion of periprostatic tissue on core biopsies in patients with clinically localized prostate cancer.
- Parameters for tumor cell proliferation rate such as MIB-1, p27, waf-p21 and apoptosis (bcl-2) could be used as a measure of tumor growth\textsuperscript{6,7}.
- Loss of expression of adhesion molecules such as E-cadherin and CD44 as an indicator for potential metastatic behavior\textsuperscript{8,9}.
- Expression of oncogenes and suppressor genes such as PTEN and TP53 as markers of uncontrolled tumor growth\textsuperscript{10,11}.

The search for prognostic markers other than grading, needs to be continued, but it should be realized that the same problems may be encountered as in histopathological grading\textsuperscript{2}.

In conclusion, for the moment we don’t dispose any absolute prognostic marker to distinguish a clinically significant from a non significant case. To be sure that a case is not significant is very important because the patient could avoid an overtreatment, which is not without consequences, some time serious, especially after radical prostatectomy.

An important parameter is the age of the patient. In a rather young man with a tiny area of cancer in one of the biopsy samples even if all the measured parameters are negative, we are obliged to advise a radical treatment, since as it is proved that we can’t exclude the presence of aggressive cancer nodules in the gland, missed in the needle biopsy. The contrary could be even unethical.

On the contrary we can be more conservative in front of a older patient with the same findings and propose him a close follow up.

The question is, who is considered to be young and who old. We arbitrary put as a border the age of 70 to 72, but this should be left on the judgement of the treating surgeon.

Another, rather ethical question is whether we should insist to detect small focuses of prostate cancer, by getting eighteen or twenty eight samples. Generally, in such cases, if they are positive, it is only a microscopic neoplastic low Gleason area in one of the tissue specimens, which, in a very high percentage, should be insignificant. The result is that the patient is unhappy, anxious for the last years of his life and the Urologist in a dilemma about the behavior he should adopt, concerning the appropriate treatment.

As a conclusion we can say that, considering all the parameters mentioned above, the practicing Urologist can be close to the answer and choose an appropriate treatment which is not always the same for every patient.
SUMMARY

Jedan od najvažnijih problema s kojima se urolog sreće u praksi je kako razlikovati klinički signifikantni od nesignifikantnog karcinoma prostate (CaP) i kako izbaci nepotrebno agresivno lečenje kod jedne grupe bolesnika, odnosno nedovoljno radikalno lečenje kod druge grupe bolesnika.

Na prvom mestu, potrebno je precizno odrediti lokalni stadijum i agresivnost bolesti, što se danas rutinski radi pomoću biopsije prostate vodjene transrektalnim ultrazvukom. Postoji nekoliko dilema vezanih za biopsiju prostate: broj iscečaka, subjektivnost patologa u određivanju Glisonovog skora, značaj prisustva PIN u materijalu multifokalni karakter rasta CaP itd. Smatramo da je šest od osam iscečaka dovoljan broj za detekciju klinički značajnog CaP i da veći broj iscečaka vodi nepotrebnoj detekciji kliničkinesignifikantnih karcinoma. Sa druge strane, Glisonov skor je obično potcenjen u bioptiranom materijalu, u odnosu na matgerijal posle radikalne prostatektomije.

Na drugom mestu, lečenje se prilagodjava prema starosti i opštem stanju bolesnika. Kod mladijeg bolesnika, mladijeg od 70-72 godine, predlaže se agresivno lečenje, čak i ako je nadjen mali uzorak CaP, samo u jednom iscečku. Sa druge strane, etičko pitanje je da li treba insistirati na detekciji malih fokusa karcinoma kod starijih ljudi i tako ih u poslednjim godinama života učiniti nesrećnim i uplašenim.

Ključne reči: signifikantni kacinom prostate, biopsija prostate, broj iscečaka, izbor metode lečenja, starost bolesnika, radikalna prostatektomija.

REFERENCES