Lisovy V. N.[1], Pilipenko I. N.[2], Pilipenko N. I.[1]

CONSCIENCE-BASED MEDICINE: NEW APPROACHES TO THE MANAGEMENT OF PROSTATE CANCER PATIENTS

Kharkiv National Medical University[1], Grigoriev Institute for Medical Radiology of NAMSU[2], Ukraine

Time to focus on patients not profit. Emphasize medicine not money … be a patient care specialty … ethics based on what is best for the patient … service to community.
R. G. Evens, 1989

…the absolute necessity for medical leadership to recognize the need for change; establish common professional values; create a vision; and provide courage, strength, and passion to make the correct strategic choices to empower the success of medicine in the future.
R. W. Holden, 1998

Abstract. *Almost half of prostate men cancer, the disease is benign and not life threatening. However, some patients with aggressive tumors have manifestations that can lead to death if not treated. Now the problem concerns to predict the nature of its course. This will prevent useless severe treatment when most patients the tumor can be controlled minimal therapeutic intervention or even just to keep the patient under regular diagnostic control. At present there are real possibilities to confidently enough differentiate the cases where a radical medical aid to the patient is needed and where either only minimal therapeutic support or even just regular periodic examinations and consultations would suffice. What is respectfully acknowledged at major meetings and in editorials is not being applied to patients. The explanations are complex and rooted in a conflict between knowledge and belief with disturbing undertones of economic self-interest. It is time to practice conscience-based medicine.*
Keywords*: prostate cancer, management of patients, conscience-based medicine.*

Prostate cancer (PC) is one of the most common men cancer. In North America early expected number of new prostate cancer cases ranges from 219,000 to 240,000 cases and from 27,000 to 31,000 deaths [1-4]. As one of the five or six men will

develop PC at some point in their lives. Incidence increases with age — more than 65% of cases are diagnosed in men of 65 and older [5, 3].

Moreover, 50% of men older than 50 years at autopsy have PC, but the probability of clinical diagnosis is only about 18%. The estimated probability of dying from PC for men is set at 2.8%, while the most common actual cause of death of men diagnosed with PC are cardiovascular diseases [6, 7]. In another autopsy study it was showed that highly differentiated prostatic intraepithelial neoplasia, which is the precursor of PC, is present in almost 86% of men aged 80 years and older [8]. In 30-50% of men who are diagnosed with PC, the disease is benign and not life threatening [9].

However, some patients with aggressive tumors have manifestations that can lead to death if not treated. Hence, early detection of aggressive forms of the disease helps to reduce mortality in the treatment of localized disease and is the only chance for successful treatment [10, 11]. Before the broad distribution of early PC detection methods, including digital rectal examination and transrectal ultrasound studies and measurements of serum PSA, in most cases PC was diagnosed in the stage of progression of the disease and the men died within a few years after diagnosis.

So now the problem concerns not only accurate diagnosis of PC, but more importantly, to predict the nature of its course. This will prevent useless severe treatment when most patients the tumor can be controlled minimal therapeutic intervention or even just to keep the patient under regular diagnostic control, which should be guaranteed by using effective methods.

R. Choo et al. [12] and L. Klotz [13] propose to determine the decision to intervene by PSA kinetics and/or histological progression of the tumor. This strategy offers the attraction of individualizing therapy based on the biological behavior of cancer. Paients with slow growing tumor will be spared the negative effects of radical treatment, while patients with rapidly progressing cancer will benefit from this therapy.

Many options for the management of patients with newly diagnosed PC are availble. Magnetic resonance imaging (MRI) plays an important role in the early

diagnosis of PC. Moreover, it helps identify the remains of the tumor after surgery or relapse after treatment, when there is clinical or biochemical suspicion of it. The feasibility to assess PC using conventional MRI, T1-and T2-weighted sequences, MR spectroscopy, diffusion-weighted imaging, and dynamic contrast enhancement MRI has been investigated. All forms of treatment to a greater or lesser extent alter the MRI features of the prostate, and it is important to be able to distinguish between the effects of treatment and recurrent or residual cancer to aid in further clinical patient management [14].

Doubts exist with respect to the benefits of a broad screening for PC. In a recently published European study has shown that screening for PC may provide a reduction in mortality from this cancer by 20%, but to avoid one death 48 patients should be radically treated [15]. This study emphasizes that although screening and early detection provide benefits in terms of reducing mortality, yet they create a significant risk of unnecessary treatment. This is a dilemma that underlies the requirement of selective treatment approach. Estimates show that 50% of men who have PC diagnosed on the basis of screening would not have any clinical symptoms of PC during their lifetime [16]. To avoid excessive treatment of patients with not an aggressive tumor, life expectancy and clinical manifestations, such as tumor stage, PSA level, and biopsy Gleason should be taken into account [9]. Currently, histopathological analysis of biopsy material obtained by transrectal ultrasonography in check is performed on a Gleason scale. This leads to an underestimation of the aggressiveness of the tumor in 26%-41% of biopsy samples compared with samples obtained at prostatectomy [17-20].

There is evidence that screening for PC by PSA serum levels reduces mortality from this disease, but this has a side effect — a high level of false-positive diagnoses. The fraction of false-positives ranged from 3.3 to 12.1% in one round, and 12.5% of men had at least one false positive result for three rounds [21]. Also indicated is that digital rectal examination, transrectal ultrasound and PSA are limited as screening tests due to-their lack of sensitivity, specificity and in efficiency costs [11, 22, 23]. PC, hyperplasia, and prostate inflammation are characterized by varying degrees of

elevated PSA levels [24-26]. The growth rate in serum PSA during the year before diagnosis (PSA speed), as shown in a number of researches, is significantly associated with the time of recurrence, cancer-specific mortality [27-29], and external beam radiotherapy [30]. In addition, conventional ultrasound, which is used for biopsy guidance, i snot accurate enough for biopsy even in the Doppler mode [31]. Contrast-enhanced transrectal ultrasound is more sensitive for the detection of malignant cells in the prostate without significant loss of specificity [32].

Researched were CT signs such as uneven edge of the prostate and obliteration of the angle between the prostate and neighboring seminal vesicles. It became apparent that CT data is neither sufficiently sensitive nor specific for the detection of tumor sprouting, compared to what is needed for making therapeutic decisions. MRI definitely has better contrast and spatial resolution than CT [33]. Many comparisons of MRI features and pathological findings are published, and the literature contains a number of MRI features for detection of extra capsular distribution tumors [34-42].

In a large study, E. Kuligowska et al. [43] determined the accuracy of PC detection by means of: (a) gray and color Doppler transrectal ultrasound, (b) excessive levels of PSA in blood serum, and (c) six fold transrectal biopsy under ultrasound control. There also was a relationship between angiogenesis in the tumor and biological activity of the tumor assessed by means of ultrasound data. Gray scale ultrasound images found 41.1% of cancer cases, while color Doppler ultrasound imaging revealed additional 15.8% (56.9% total) cases. By using biopsy 56.8% of cancer cases were found, while a six fold biopsy revealed 43.2% more cancer cases (100% total). Tumor hypervascularization that was determined by color Doppler ultrasonography correlates with biological aggressiveness of tumors. PSA level was normal in 30.5% of patients with PC. The authors concluded that gray scale transrectal ultrasound even in combination with color Doppler ultrasound is insufficient for PC screening, so biopsy should always be accompanied by a selection of six biopsy samples.

Anatomical and metabolic prostate mapping with MR spectroscopy make it possible to optimize treatment planning (expectant management, surgery, or

radiotherapy- intensity-modulated or brachytherapy), and, therefore, to further expand the role of MRI in achieving a truly individual approach to the patient management [44].

M. McNaughton-Collins et al. [11] studied the effect of pelvic irradiation on the serum PSA. Patients received irradiation at a total dose of 50.4 Gy or more (1.8 Gy per fraction) and 25.0 Gy with fractions of 5.0 Gy. Rapid rise in PSA level was found during the first 3 weeks (up to 3.7-fold increase compared to the initial). At the end of treatment PSA level was almost no different from the initial, and later declined to 77%.

Thus, it can be noted that at present there are real possibilities to confidently enough differentiate the cases where a radical medical aid to the patient is needed and where either only minimal therapeutic support or even just regular periodic examinations and consultations would suffice. Methods of the disease treatment vary widely from observation without intervention to a very aggressive surgery or radiation therapy, which is currently available in several variants. There is much debate regarding the best or most acceptable treatment for different stages of the disease.

Management options are numerous. A recent study of the primary treatment received by 11,892 men with newly diagnosed PC showed that in approximately 7% of cases active surveillance was elected, 50% — radical prostatectomy, 12% — external beam radiation therapy (RT), 13% — brachytherapy, 4% — cryoablation, and 14% — androgen deprivation therapy [45]. Other treatments, such as high-intensity focused ultrasound and photodynamic therapy are also becoming increasingly available. Continuous improvement and refinancing of these treatment strategies, along with the trend towards early detection and reduction in PC stage at diagnosis led to a 99% relative survival at 5 years after diagnosis [5]. However, some patients showed recurrence of the tumor, which is often suspected based on digital rectal examination or PSA levels increase. MRI may play an important role in the evaluation of these patients. The choice of treatment depends on several factors, including the probability of accurate diagnosis of PC, the degree of histological

aggressiveness of the tumor, the age and overall health, including co-morbidities, as well as the expected results and possible side effects associated with different forms of treatment [46-48].

The optimal treatment for men with PC remains controversial for several reasons. First, the possibility of setting an accurate diagnosis, so that imaging cannot always identify metastatic PC. Second, the Gleason grade, which is one of the most important factors predicting disease progression, is subjective and depends on the interpretation of the present biopsy material by pathologist [49]. Third, screening for PC based on PSA is not always certain. Fourth, an important consideration in the choice of treatments given is the quality of life [50, 51]. Finally, given that most patients with PC are men of advanced age, aging population makes it important to carefully examine the results of treatment, so that they can have a very significant impact on the overall health of the population. In this sense, the use of large databases is extremely valuable and powerful resource for epidemiological studies because the general population is more heterogeneous compared with hospitals or centers of observational studies [52].

L.M. Franks [6] evaluated the results of a waiting strategy with selective delayed intervention and using the definition of PSA progression or histological signs as indications for early treatment of clinically localized PC. Active surveillance for localized PC of low degree of aggressiveness may reduce the risk of over-treatment of clinically insignificant tumors, while preserving the possibility of definitive therapy for those patients who are transferred over time into the category of high risk.

There are several treatment options for localized PC: radical prostatectomy, brachytherapy, external beam radiation therapy, androgen deprivation therapy and active surveillance [52-55]. E. H. Zhou et al. [52] studied the relationship between disease specific survival and the four standard methods of treatment (radical prostatectomy, brachytherapy, external beam radiotherapy, androgen therapy) and observation without treatment within 6 months after the diagnosis of PC. The study included 10,179 men aged 65 years and older with prostate cancer cases diagnosed between 1999 and 2001, and the follow up to 2005. Treatments were clinically

acceptable treatment options for the disease. It was shown in this population-based study that radical prostatectomy and brachytherapy is associated with improved survival of patients.

One of the standard treatments for locally advanced disease is a radical course of external beam radiotherapy combined with androgenic suppression. Large multi center randomized trials in Europe [56] and North America [57] showed a high level of disease-free survival when using this approach.

Brachytherapy alone or combined with external beam radiotherapy has been widely recognized as a first line treatment for patients with localized prostate cancer [58-60].

N. Pervez, et al. [61] studied the acute toxicity of intensity modulated radiation therapy combined with androgen deprivationin patients with high risk PC. The total local dose was 68 Gy in 25 fractions (2.72 Gy/fraction) for 5 weeks. Irradiated were prostate and seminal vesicles. Simultaneously, pelvic lymph nodes received 45 Gy in 25 fractions. For the treatment of patients a tomotherapy unit with intensity modulation was used. Manifestations of acute toxicity were recorded weekly during treatment and in 3 months at the end. Maximum acute toxicity was as follows: 35% of patients had grade 2 toxicity of the gastrointestinal tract, 6.67% of patients had grade 3 and 33.33% grade 2 of the genitourinary toxicity. Three months after radiotherapy (RT) the toxicity significantly decreased. Therefore, the investigated mode of combined hormonal and radiation therapy is well tolerated.

C. R. King a. D. S. Kapp [62] consider, that after radical prostatectomy the actual doses radical irradiation of prostate bed for both adjuvant radiotherapy (ART) and salvage radiotherapy (SRT) have to be in the range of 60–70 Gy. Greater doses would potentially achieve significantly greater disease-free tumor control rates. ART is radiotherapy which is performed in the immediate postoperative setting, and SRT is performed after a demonstrated in any way (e.g., biochemical) recurrence. ART and SRT offer the potential for radical treatment after unsuccessful prostatectomy (PE). Two randomized studies have demonstrated an improvement in disease-free survival for ART after PE in patients at high risk, defined as pT3 or positive surgical

margin [63, 64]. The positive role of SRT with biochemical relapse after PE has also been demonstrated in numerous studies [66, 67]. In two studies of ART, the total dose to the tumor bed was 60 Gy [64] and 60-64 Gy [65]. For SRT the American Society of Therapeutic Radiology and Oncology has consensus to recommend high doses of radiation, at least 64 Gy in the normal fractionation [68]. There is ample evidence to support dose escalation to 78 Gy for radical RT in localized prostate tumors [69-73].

However, the results of the many studies have shown that acute rectal reaction depends on the dose and the degree of manifestations is also linked. Postoperative RT leads to more acute manifestations of gastrointestinal toxicity than radical RT alone. For postoperative RT it is wise to use various restrictions in dose [74].

RT and RPE are widely accepted treatments for clinically localized prostate cancer. Although these methods have comparable results, a large number of patients who choose RP eventually pass RT [75, 76] either in the adjuvant or salvage form. Depending on the pathological results (e.g., extra capsular penetration, seminal vesicles invasion, positive surgical edges) patients undergoing initial primary RPE may need ART with or without hormone therapy. ART is often administered after RPE to patients with high risk (e.g., extra capsular penetration, seminal vesicles invasion, positive surgical edge, high pT or high Gleason grade) and as has been shown to reduce the risk for metastasis and biochemical recurrence in men with positive the pathological results of the RPE [76]. In addition, patients who initially had RPE then may be subjected to SRT through sustainable growth PSA as biochemical sign of recurrence. The question of whether the RT should be performed immediately or postpone on term for improving the PSA remains controversial [76, 77]. The choice between these treatments (RT with or without hormone therapy, primary RPE plus ART) is largely dependent on their adverse effects and benefits for the patient.

Common side effects of normal tissue as complication of RT include lesions of the rectum and/or bladder. Both acute and late lesions of the gastrointestinal tract and urogenital system after high dose RT were documented. Since toxicity may

eventually become more significant, acute toxicity is an important predictor of late toxicity. Since toxicity may eventually become more significant, acute toxicity is an important predictor of late toxicity [78–82]. Acute side effects can be very serious and lead to interruption of the planned treatment in 10% of patients [83].

Permanent brachytherapy with I-125 and Pd-103 implants at high biologically effective dose of 200 Gy gives 96.9% local control of PC [84]. One of the important benefits of permanent implantation of radioactive grains in the tumor is a very conformal high dose of irradiation to the prostate gland. High doses, as it shown above, are necessary for malignant tumor eradication and significantly reduce the likelihood of biochemical (level PSA) recurrence of the tumor [85, 86]. Therefore various brachytherapy schemes are often used to control tumors in all stages. The results of treatment are usually evaluated by means of biochemical control [87]. The problem of using PSA as an endpoint of a positive treatment outcome is that it does not distinguish between those patients with a systemic recurrence compared to local. In the past, digital rectal examination was used to assess local control. Currently accepted is that prostate biopsy is the best method for determining residual or recurrent local disease [85].

In an editorial in the "Journal of clinical oncology" Anthony Zietman [88] from Harvard Medical School wrote: «What began as a small crack in the solid concept of early detection and early treatment for prostate cancer has now widened and spread. Despite imperfections which limit their interpretation, the recently published randomized screening trials show there is only a small — or even no — improvement in survival from early detection over the first 10 years [15, 89]. One trial also showed that the number of patients (around 50) that must be treated to save one life is alarmingly high [89]. These data come at a time when medical spending, long recognized to be beyond the nation’s means, is to be tightened and restructured along evidence-based guidelines with care being directed preferentially toward areas of proven benefit. The Institute of Medicine has drawn up national priorities for comparative effectiveness research, and the management of localized prostate cancer sits squarely in the first quartile [90]. Indeed, it is the top-ranking oncologic priority.

A perfect storm of clinical evidence and economic reality has arisen in which urologists and radiation oncologists need to examine the evidence, examine their souls, and start to carefully look at every new patient asking, before anything else — is treatment really needed at all? If it is not, and that will frequently be the answer, then they must be prepared to lead the patient along the less financially rewarding and decidedly unglamorous path of active surveillance. The training of resident doctors has to date been so focused on cure, and the culture of early detection/early treatment so deeply ingrained, that it is little wonder that this shift in thinking is yet to reflect itself in everyday practice. What is respectfully acknowledged at major meetings and in editorials is not, in the daily reality of the clinic, being applied to patients. Indeed, in the United States, the proportion of men being managed conservatively has actually been declining [92]. The explanations, as hinted, are complex and rooted in a conflict between knowledge and belief with disturbing undertones of economic self-interest. It is time to practice conscience-based medicine.

References.

1. Jemal A., Siegel R., Xu J., Ward E. Cancer statistics, 2010. CA Cancer J Clin, 2010, vol. 60, pp. 277–300.
2. American Cancer Society. Cancer facts and figures, 2007. Atlanta, GA: ACS; 2007.
3. Jemal A., Siegel R., Ward E., et al. Cancer statistics, 2007. CA Cancer J Clin, 2007, vol. 57, pp. 43–66.
4. Canadian Cancer Society / National Cancer Institute of Canada, National Cancer Institute of Canada. In: Canadian cancer statistics. Toronto: National Institute of Cancer; 2008.
5. Jemal A., Siegel R., Xu J., Ward E. Cancer statistics, 2010. CA Cancer J Clin, 2010, vol. 60, P. 277–300. [Published correction appears in CA Cancer J Clin, 2011, vol. 61, pp. 133–134.]
6. Franks L.M. Proceedings: Etiology, epidemiology, and pathology of prostatic cancer. Cancer, 1973, vol. 32, pp. 1092–1095.
7. Hølund B. Latent prostatic cancer in a consecutive autopsy series. Scand J Urol Nephrol, 1980, vol. 14, pp. 29-35.
8. Sakr WA, Grignon DJ, Haas GP, et al. Epidemiology of high grade prostatic intraepithelial neoplasia. Pathol Res Pract, 1995; vol. 191, pp. 838–841.
9. Walsh P.C., DeWeese T.L., Eisenberger M.A. Clinical practice: localized

prostate cancer. N Engl J Med, 2007; vol. 357, pp. 2696–2705.
10. American Cancer Society. Prostate cancer. Atlanta, Ga: American Cancer Society, 1999.
11. McNaughton-Collins M., Ransohoff D.F., Barry M.J. Early detection of prostate cancer: serendipity strikes again., 1997, vol. 278, pp. 1516–1519.
12. Choo R., Klotz L., Danjoux C., et al: Feasibility study: Watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. J Urol, 2002, vol. 167, pp. 1664–1669.
13. Klotz L: Active surveillance for prostate cancer: For whom? J Clin Oncol, 2005, vol. 23, pp. 8165–8169.
14. Vargas H. A., Wassberg C., Akin O., Hricak H. MR Imaging of Treated Prostate Cancer. Radiology, 2012; vol. 262, pp. 26 –42.
15. Schroder F.H., Hugosson J., Roobol M.J., et al: Screening and prostate-cancer mortality in a randomized European study. N Engl J Med, 2009, vol. 360, pp. 1320–1328.
16. Draisma G., Boer R., Otto S.J., et al. Lead times and overdetection due to prostatespecific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst, 2003, vol. 95, pp. 868–878.
17. Kvele R., Mцller B., Wahlqvist R., et al. Concordance between Gleason scores of needle biopsies and radical prostatectomy specimens: a population-based study. BJU Int, 2009, vol. 103, pp. 1647–1654.
18. Divrik R.T., Eroglu A., Sahin A., Zorlu F., Ozen H. Increasing the number of biopsies increases the concordance of Gleason scores of needle biopsies and prostatectomy specimens. Urol Oncol, 2007, vol. 25, pp. 376–382.
19. Tomioka S., Nakatsu H., Suzuki N., Murakami S., Matsuzaki O., Shimazaki J. Comparison of Gleason grade and score between preoperative biopsy and prostatectomy specimens in prostate cancer. Int J Urol, 2006, vol. 13, pp. 555–559.
20. Rajinikanth A., Manoharan M., Soloway C.T., Civantos F.J., Soloway M. S. Trends in Gleason score: concordance between biopsy and prostatectomy over 15 years. Urology, 2008, vol. 72, pp. 177–182.
21. Kilpelainen T.P., Tammela T.L.J., Maattanen L., et al. False-positive screening results in the Finnish prostate cancer screening trial. British Journal of Cancer, 2010, vol. 102, pp. 469–474.
22. Benson M.C., McMahon D.J., Cooner W.H., Olsson C.A. An algorithm for prostate cancer detection in a patient population using prostate specific antigen and prostate specific antigen density. World J Urol, 1993, vol. 11, pp. 206–213.
23. Lee F., Torp-Pedersen S.T., Siders D.B., et al. Transrectal ultrasound in the diagnosis and staging of prostatic carcinoma. Radiology, 1989, vol. 170, pp. 609–615.
24. Lee F., Littrup P.J., Torp-Pedersen S.T., et al. Prostate cancer: comparison of transrectal US and digital rectal examination for screening. Radiology, 1988, vol. 168, pp. 389–394.
25. Lee F., Littrup P.J., Loft-Christensen L., et al. Predicted prostate specific antigen

results using transrectal ultrasound gland volume: differentiation of benign prostatic hyperplasia and prostate cancer. Cancer, 1992, vol. 70, pp. 211–220.
26. Lee F., Littrup P.J. The role of digital rectal examination, transrectal ultrasound, and prostate specific antigen for the detection of confined and clinically relevant prostate cancer. J Cell Biochem Suppl, 1992, vol. 16, pp. 69–73.
27. D'Amico A.V., Chen M., Roehl K., et al: Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. N Engl J Med, 2005, vol. 351, pp. 125–135.
28. Sengupta S., Myers R.P., Slezak J.M., et al: Preoperative prostate-specific antigen doubling time and velocity are strong and independent predictors of outcomes following radical prostatectomy. J Urol, 2005, vol. 174, pp. 2191–2196.
29. Patel D.A., Presti J.C., McNBeal J.E., et al: Preoperative PSA velocity is an independent prognostic factor for relapse after radical prostatectomy. J Clin Oncol, 2005, vol. 23, pp. 6157–6162.
30. D'Amico A.V., Renshaw A.A., Sussman B., et al: Pretreatment PSA velocity and risk of death from prostate cancer following external beam radiation therapy. JAMA, 2005, vol. 294, pp. 440–447.
31. Cornud F., Belin X., Piron D., et al. Color Doppler-guided prostate biopsies in 591 patients with an elevated serum PSA level: impact on Gleason score for non-palpable lesions. Urology, 1997, vol. 49, pp. 709–715.
32. Halpern E. J., Rosenberg M., Gomella L. G. Prostate Cancer: Contrastenhanced US for Detection. Radiology, 2001, vol. 219, pp. 219–225.
33. Lawton C. A., Grignon D., Newhouse J. H., et al. Prostatic Carcinoma. RadioGraphics, 1999, vol. 19, pp. 185–203.
34. Perrotti M., Kaufman R.P., Jennings T.A., et al. Endo-rectal coil magnetic resonance imaging in clinically localized prostate cancer: is it accurate? J Urol, 1996, vol. 156, pp.106–109.
35. Huch Boni R.A., Boner J.A., Debatin J.F., et al. Optimization of prostate carcinoma staging: comparison of imaging and clinical methods. Clin Radiol, 1995, vol. 50, pp. 593–600.
36. Giri P.G., Walsh J.W., Hazra T.A., Texter J.H., Koontz W.W. Role of computed tomography in the evaluation and management of carcinoma of the prostate. Int J Radiat Oncol Biol Phys, 1982, vol. 8, pp. 283–287.
37. Chelsky M.J., Schnall M.D., Seidmon E.J., Pollack H.M. Use of endorectal surface coil magnetic resonance imaging for local staging of prostate cancer. J Urol, 1993; vol. 150, pp. 391–395.
38. Jager G.J, Barentsz J.O., de la Rosette J.J., Rosenbusch G. Preliminary results of endorectal surface coil magnetic resonance imaging for local staging of prostate cancer. Radiology, 1994, vol. 34, pp. 129–133.
39. McSherry S.A., Levy F., Schiebler M.L., Keefe B., Dent G.A., Mohler J.L. Preoperative prediction of pathological tumor volume and stage in clinically localized prostate cancer: comparison of digital rectal examination, transrectal ultrasonography, and magnetic resonance imaging. J Urol, 1991, vol. 146, pp. 85–89.
40. Chefchaouni M.C., Flam T., Cornud F., et al. Results of endorectal MRI in local

staging of prostatic cancer: correlation with specimens from prostatectomy — apropos of 47 cases. J Urol, 1996, vol. 102, pp. 51–55.
41. Bartolozzi C., Menchi I., Lencioni R., et al. Local staging of prostate carcinoma with endorectal coil MRI: correlation with whole-mount radical prostatectomy specimens. Eur Radiol, 1996, vol. 6, pp. 339–345.
42. Bates T.S., Cavanagh P.M., Speakman M., Gillatt D.A. Endorectal MRI using a 0.5 T mid-field system in the staging of localized prostate cancer. Clin Radiol, 1996, vol. 51, pp. 550–553.
43. Kuligowska E., Barish M. A., Fenlon H. M., Blake M.. Predictors of Prostate Carcinoma: Accuracy of Gray-Scale and Color Doppler US and Serum Markers. Radiology, 2001, vol. 220, pp. 757–764.
44. Claus F. G., Hricak H., Hattery R. R.. Pretreatment Evaluation of Prostate Cancer: Role of MR Imaging and ^{1}HMR Spectroscopy. RadioGraphics, 2004, vol. 24, S167–S180.
45. Cooperberg M.R., Broering J.M., Carroll P.R. Time trends and local variation in primary treatment of localized prostate cancer. J Clin Oncol, 2010, vol. 28, pp. 1117–1123.
46. Potters L., Klein E.A., Kattan M.W., et al. Monotherapy for stage T1-T2 prostate cancer: Radical prostatectomy, external beam radiotherapy, or permanent seed implantation. Radiother Oncol, 2004, vol. 71, pp. 29–33.
47. Ciezki J.P., Klein E.A., Angermeier K., et al. A retrospective comparison of androgen deprivation (AD) vs. no AD among lowrisk and intermediate-risk prostate cancer patients treated with brachytherapy, external beam radiation therapy, or radical prostatectomy. Int J Radiat Oncol Biol Phys, 2004, vol. 60, pp. 1347–1350.
48. Roemeling S., Roobol M.J., Postma R., et al. Management and survival of screen-detected prostate cancer patients who might have been suitable for active surveillance. Eur Urol, 2006, vol. 50, pp. 475–482.
49. Bracarda S., de Cobelli O., Greco C., et al. Cancer of the prostate. Crit Rev Oncol Hematol., 2005, vol. 56, pp. 379–396.
50. Bill-Axelson A., Holmberg L., Ruutu M., et al. Radical prostatectomy versus watchful waiting in early CaP. N Engl J Med, 2005, vol. 352, pp. 1977–1984.
51. Steineck G., Helgesen F., Adolfsson J., et al. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med, 2002, vol. 347, pp. 790–796.
52. Zhou E. H., Ellis R. J., Cherullo E., Colussi V., Fang Xu, Wei-Dong Chen et al. Radiotherapy and survival in prostate cancer patients: a population-based study. Int. J. Radiation Oncology Biol. Phys., 2009, vol. 73, pp. 15–23.
53. Thompson I., Thrasher J.B., Aus G., et al. Guideline for the management of clinically localized prostate cancer: 2007 update. J Urol, 2007, vol. 177, pp. 2106–2131.
54. Wilt T.J., Macdonald R., Rutks I., et al. Systematic review: The comparative effectiveness and harms of treatments for clinically localized prostate cancer. Ann Intern Med., 2008, vol. 148, pp. 435–448.
55. D'Amico A.V., Whittington R., Malkowicz S.B., et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation

therapy for clinically localized prostate cancer. JAMA, 1998, vol. 280, pp. 969–974.
56. Bolla M., Collette L., Blank L., et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): A phase III randomised trial. Lancet, 2002, vol. 360, pp. 103–106.
57. Hanks G.E., Pajak T.F., Porter A., et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: The radiation therapy oncology group protocol 92-02. J Clin Oncol, 2003, vol. 21, pp. 3972–3978.
58. Sylvester J.E., Blasko J.C., Grimm P.D., et al. Ten year biochemical relapse-free survival after external beam radiation and brachytherapy for localized prostate cancer: The Seattle experience. Int J Radiat Oncol Biol Phys, 2003, vol. 57, pp. 944–952.
59. Potters L., Morgenstern C., Calugaru E., et al. 12-year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. J Urol, 2005, vol. 173, pp. 1562–1566.
60. Zelefsky M.J., Yamada Y., Fuks Z., et al. Long-term results of conformal radiotherapy for prostate cancer: Impact of dose escalation on biochemical tumor control and distant metastasesfree survival outcomes. Int J Radiat Oncol Biol Phys, 2008, vol. 71, pp. 1028–1033.
61. Pervez N., Small C., Mackenzie M., et al. Acute toxicity in high risk prostate cancer patients treated with androgen suppression and hypofractionated intensity-modulated radiotherapy. Int. J. Radiation Oncology Biol. Phys., 2010, vol. 76, pp. 57–64.
62. King C. R., Kapp D. S. Radiotherapy after prostatectomy: is the evidence for dose escalation out there? Int. J. Radiation Oncology Biol Phys, 2008, vol. 71, pp. 346– 350.
63. Bolla M., van Poppel H., Collette L., et al. Postoperative radiotherapy after radical prostatectomy: A randomized controlled trial (EORTC trial 22911). Lancet, 2005, vol. 366, pp. 572–578.
64. Thompson I. M., Tangen C. M., Paradelo J., et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: A randomized trial. JAMA, 2006, vol. 296, pp. 2329–2335.
65. Stephenson A. J., Scardino P. T., Kattan M. W., et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol, 2007, vol. 25, pp. 2035–2041.
66. Hayes S. B., Pollack A. Parameters for treatment decisions for salvage radiation therapy. J Clin Oncol, 2005, vol. 23, pp. 8204–8211.
67. Cox J. D., Gallagher M. J., Hammond E. H., et al. for the ASTRO Consensus Panel. Consensus statement on radiation therapy of prostate cancer: Guidelines for prostate re-biopsy after radiation and for radiation therapy with rising PSA levels after radical prostatectomy. J Clin Oncol, 1999, vol. 17, pp. 1155–1163.
68. Pollack A., Zagars G. K., Starkschall G., et al. Prostate cancer radiation dose–response: Results of the M. D. Anderson phase III randomized trial. Int J Radiat

Oncol Biol Phys, 2002, vol. 53, pp. 1097–1105.
69. Zietman A. L., DeSilvio M. L., Slater J. D., et al. Comparison of conventional dose vs high dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: A randomized controlled trial. JAMA, 2005, vol. 294, pp. 1233–1239.
70. Eade T. N., Hanlon A. L., Horwitz E. M., et al. What dose of external beam radiation is high enough for prostate cancer? Int J Radiat Oncol Biol Phys, 2007, vol. 68: pp. 682–689.
71. Zelefsky M. J., Leibel S. A., Gaudin P. B., et al. Dose-escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. Int J Radiat Oncol Biol Phys, 1998, vol. 41, pp. 491–500.
72. Valicenti R. K., Gomella L. G., Ismail M., et al. Effect of higher radiation dose on biochemical control after radical prostatectomy for pT3N0 prostate cancer. Int J Radiat Oncol Biol Phys, 1998, vol. 42, pp. 501–506.
73. Anscher M. S., Clough R., Dodge R. Radiotherapy for a rising PSA after radical prostatectomy: The first 10 years. Int J Radiat Oncol Biol Phys, 2000, vol. 48, pp. 369–375.
74. Cheng J. C., Schultheiss T. E., Nguyen K. H., Wong J. Y. C.. Acute toxicity in definitive versus postprostatectomy image-guided radiotherapy for prostate cancer. Int. J. Radiation Oncology Biol Phys, 2008, vol. 71, pp. 351–357.
75. Kupelian P.A., Potters L., Khuntia D., et al. Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy > or =72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. Int J Radiat Oncol Biol Phys, 2004, vol. 58, pp.25–33.
76. Swanson G.P., Hussey M.A., Tangen C.M., et al. Predominant treatment failure in postprostatectomy patients is local: Analysis of patterns of treatment failure in SWOG 8794. J Clin Oncol, 2007, vol. 25, pp. 2225–2229.
77. Bolla M., van Poppel H., Collette L., et al. Postoperative radiotherapyafter radical prostatectomy: A randomised controlled trial (EORTC trial 22911). Lancet, 2005, vol. 366, pp. 572–578.
78. Skwarchuk M.W., Jackson A., Zelefsky M.J., et al. Late rectal toxicity after conformal radiotherapy of prostate cancer (I): Multivariate analysis and dose-response. Int J Radiat Oncol Biol Phys, 2000, vol. 47, pp. 103–113.
79. Kupelian P.A., Reddy C.A., Carlson T.P., et al. Dose/volume relationship of late rectal bleeding after external beam radiotherapy for localized prostate cancer: Absolute or relative rectal volume? Cancer J, 2002, vol. 8, pp. 62–66.
80. O'Brien P.C., Franklin C.I., Poulsen M.G. et al., for the Trans-Tasman Radiation Oncology Group. Acute symptoms, not rectally administered sucralfate, predict for late radiation proctitis: Longer term follow-up of a phase III trial. Int J Radiat Oncol Biol Phys, 2002, vol. 54, pp. 442–449.
81. De Meerleer G., Vakaet L., Meersschout S., et al. Intensitymodulated radiotherapy as primary treatment for prostate cancer: Acute toxicity in 114 patients. Int J Radiat Oncol Biol Phys, 2004, vol. 60, pp. 777–787.
82. Schultheiss T.E., Lee W.R., Hunt M.A., et al. Late GI and GU complications in the treatment of prostate cancer. Int J Radiat Oncol Biol Phys, 1997, vol. 37, pp. 3–

11.
83. Yeoh E.E., Botten R., Russo A., et al. Chronic effects of therapeutic irradiation for localized prostatic carcinoma on anorectal function. Int J Radiat Oncol Biol Phys, 2000, vol. 47, pp. 915–924.
84. Stone N. N., Stock R. G., Cesaretti J. A., Unger P.. Local control following permanent prostate brachytherapy: effect of high biologically effective dose on biopsy results and oncologic outcomes. Int. J. Radiation Oncology Biol Phys, 2010, vol. 76, pp. 355–360.
85. Stone N.N., Stock R.G., Unger P. Intermediate-term biochemical and local control following I-125 brachytherapy for prostate cancer. J Urol, 2005, vol. 173: pp. 803–807.
86. Stock R.G., Cahlon O., Cesaretti J., et al. Combined modality treatment in the management of high risk prostate cancer. Int J Radiat Oncol Biol Phys, 2004; vol. 59: pp. 1352–1359.
87. Cox J.D, Grignon D.J, Kaplan R.S. Consensus statement: guidelines for PSA following radiation therapy. Int J Radiat Oncol Biol Phys, 1997, vol. 37, pp. 1035–1041.
88. Zietman A. Evidence-Based Medicine, Conscience-Based Medicine, and the Management of Low-Risk Prostate Cancer. J. clin oncology, 2009, vol. 24, pp. 4935–4936.
89. Andriole G.L., Crawford E.D., Grubb R.L., et al: Mortality results from a randomized prostate cancer screening trial. N Engl J Med, 2009, vol. 360, pp. 1310–1319.
90. Cooperberg M. R., Lubeck D.P., Meng M.V., et al: The changing face of low-risk prostate cancer: Trends in clinical presentation and primary management. J Clin Oncol, 2004, vol. 22, pp. 2141–2149.

Реферат. Майже у половини хворих на рак простати, хвороба протікає доброякісно і не загрожує життю. Але у деяких пацієнтів пухлини бувають з агресивними проявами і можуть призвести до смерті,якщо не лікуються. Таким чином, наразі ставиться проблема прогнозувати характер її перебігу. Це дасть можливість запобігти марного тяжкого лікування у випадках, коли у більшості хворих пухлину можна контролювати мінімальним терапевтичним втручанням або навіть вести хворого лише під регулярним діагностичним контролем. Наразі існують реальні можливості достатньо впевнено диференціювати випадки захворювання, коли не обхідна радикальна лікувальна допомога хворому від тих, що потребують або мінімальну терапевтичну підтримку, або ж лише регулярний періодичний огляд і консультацію. Але те, що з повагою визнано на великих нарадах та в редакційних статтях, не стало повсякденною клінічною реальністю. Поясненняє складним і йде корінням у конфлікт між знанням і вірою з тривожним відтінком економічних інтересів. Настав час медицини, заснованої на сумлінні.
Ключові слова: рак простати, ведення хворого, сумлінна медицина

Реферат. Примерно у половины заболевших раком простаты болезнь протекает доброкачественно и не угрожает жизни. Но у некоторых пациентов опухоль имеет агрессивное течение и может привести к смерти, если не лечить. Следовательно, ныне проблема состоит в прогнозировании характера заболевания. Это дает возможность избежать для большинства больных тяжкого лечения, контролируя опухоль только минимальными средствами, или даже ведя больного лишь под регулярным активным наблюдением. Ныне существуют возможности достаточно уверенно дифференцировать случаи заболевания, когда действительно не обходима радикальная лечебная помощь больному, от тех, когда нужна минимальная терапевтическая поддержка или даже всего лишь регулярное периодическое обследование и консультации. Тем не менее, то, что признано на широких совещаниях специалистов и в редакционных статьях, не стало широкой клинической реальностью. Найти объяснение этому явлению сложно, и уходит оно корнями, вероятно, в конфликт между знанием и верой с тревожным оттенком экономических интересов. Пришло время медицины совести.

Ключевые слова: рак простаты, ведение больного, основанная на совести медицина.

Received: 5.6.2014 *Accepted: 19.11.2014*