9. Keswani ES, Venkateshwar G. Odontogenic Maxillofacial Space Infections: A 5-Year Retrospective Review in Navi Mumbai. J Maxillofac Oral Surg. 2019;18(3):345–353. doi: 10.1007/s12663-018-1152-x.

10. Monavarian M, Kader S, Moeinzadeh S, Jabbari E. Regenerative Scar-Free Skin Wound Healing. Tissue Eng Part B Rev. 2019;25(4):294–311. doi: 10.1089/ten.TEB.2018.0350.

11. Scheepens KMJ, Marsidi N, Genders RE, Horeman-Franse T. The Compressiometer: Toward a New Skin Tensiometer for Research and Surgical Planning. IEEE J Transl Eng Health Med. 2021; 10:2500109. doi: 10.1109/JTEHM.2021.3133485.

12. Avetikov DS, Yeroshenko HA, Skrypnyk VM. Morfofunktsionalne obhruntuvannya profilaktyky pislyaoperatsiynykh keloyidnykh rubtsiv oblychchya ta shyyi. Svit medytsyny ta biolohiyi. 2013; 1:85–87. [in Ukrainian]

13. Taub D, Yampolsky A, Diecidue R, Gold L. Controversies in the Management of Oral and Maxillofacial Infections. Oral Maxillofac Surg Clin North Am. 2017;29(4):465–473. doi: 10.1016/j.coms.2017.06.004.

14. Knowles A, Glass DA 2nd. Keloids and Hypertrophic Scars. Dermatol Clin. 2023;41(3):509-517. doi: 10.1016/j.det.2023.02.010.

15. Wang PH, Huang BS, Horng HC, Yeh CC, Chen YJ. Wound healing. J Chin Med Assoc. 2018;81(2):94–101. doi: 10.1016/j.jcma.2017.11.002.

Стаття надійшла 23.04.2022 р.

#### DOI 10.26724/2079-8334-2023-2-84-105-108 UDC 616.65-006.6-089

M.P. Melnychuk

State Institution of Science "Research and practical center of preventive and clinical medicine", State administrative department, Kviv

## CHOICE OF TREATMENT IN PATIENTS WITH COMBINED PROSTATE INTRAEPITHELIAL NEOPLASIA OF PERIPHERIC AND CENTRAL ZONES

e-mail: maksymmelnychuk1980@gmail.com

The article deals with the problem of prostate intraepithelial neoplasia treatment as a precancerous state. Data of treatment results of 130 patients with prostate intraepithelial neoplasia of peripheric and central zones are analysed. Patients were distributed to groups depending on treatment method: active surveillance, Dutasteride treatment, transurethral prostate resection, and a combination of Dutasteride and transurethral prostate resection. Results were assessed after 3 years of follow-up by detecting of prostate cancer incidence. It was determined that in the active surveillance group prostate cancer rate was 68.8 %. Treatment in patients with prostate intraepithelial neoplasia of peripheric and central zones with Dutasteride decreased prostate cancer rate by 53.8 %, transurethral prostate resection decreased prostate cancer rate by 55.5 % and a combination of Dutasteride and transurethral prostate cancer rate by 54.5 %. Obtained data demonstrate the effectiveness of prostate cancer chemoprevention by prostate intraepithelial neoplasia treatment.

Key words: prostate intraepithelial neoplasia, Dutasteride, transurethral prostate resection.

### М.П. Мельничук

# ВИБІР МЕТОДУ ЛІКУВАННЯ У ПАЦІЄНТІВ З ПОЄДНАНОЮ ПРОСТАТИЧНОЮ ІНТРАЕПІТЕЛІАЛЬНОЮ НЕОПЛАЗІЄЮ ПЕРИФЕРИЧНОЇ ТА ЦЕНТРАЛЬНОЇ ЗОН

Стаття стосується проблеми лікування простатичної інтраепітеліальної неоплазії як передракового процесу. Аналізуються дані результатів лікування 130 пацієнтів з простатичною інтраепітеліальною неоплазією периферичної та центральної зон. Пацієнти розподілялися на групи в залежності від виду одержаного лікування: динамічне спостереження, прийом Дутастериду, трансуретральна резекція простати, поєднання Дутастериду та трансуретральної резекції простати. Результати оцінювалися впродовж 3-річного періоду спостереження по частоті виявлення раку передміхурової залози. Встановлено, що у випадках динамічного спостереження малігнізація відбувається у 68,8 % пацієнтів. Лікування у пацієнтів з простатичною інтраепітеліальною неоплазією периферичної та центральної зон простати у вигляді Дутастериду зменшує частоту виявлення раку передміхурової залози на 53,8 %, трансуретральна резекція простати зменшує частоту раку передміхурової залози на 55,5 %, комбіноване лікування із застосуванням Дутастериду та трансуретральної резекції простати зменшує частоту раку передміхурової залози на 54,5 %. Одержані дані свідчать про ефективність хіміопрофілактики раку передміхурової залози шляхом лікування простатичної інтраепітеліальної неоплазії. **Ключові слова:** простатична інтраепітеліальна неоплазія, дутастерид, трансуретральна резекція простати.

The study is a fragment of the research project "Optimization of surgical treatment of patients under the program of quick recovery on the base of mini-invasive surgery improvement, in particular with the use of nanobiosensitive technologies", number of state registration No. 0122U000233.

Prostate intraepithelial neoplasia (PIN) is considered to be a precancerous state and an actual medical and social problem in the whole world. The study of prostate pathology is connected with the investigation of morphofunctional features of normal men's reproductive system, which gives an opportunity for better understanding of malformations and functional disorders of different organs of the reproductive system [1].

© M.P. Melnychuk, 2023

According to WHO data, the incidence of prostate cancer (PC) in the world is 1000000 and mortality rate is about 300000 [5]. One of the ways to improve early diagnostics and treatment results of PC is PIN detection. Currently there is no agreed position among practical urologists as well as investigators about prognosis in patients with PIN [14]. Active PIN treatment (surgical, radiation therapy) is not supported by majority of scientists [12]. At the same time high progression rate from PIN to PC influenced on chemoprevention study [13].

According to R. Montironi definition, chemoprevention of precancerous states of prostate, such as PIN, is directed at ending or regression of cancerogenesis by insertion of one or several non toxic chemical compounds [9]. The ultimate goal is PIN regression and decrease of PC incidence [2]. Difficulties in chemopropevention studies are connected with necessity of long-term surveillance of large cohorts of practically healthy men and represent organizational and economical hardships. Therefore, clinical studies in chemoprevention field are limited by pilot ptojects with limited number of patients of risk group (PIN) [3].

Controversual use of 5-alphareductase inhibitors as a PC chemoprevention method was investigated in randomized studies – The Prostate Cancer Prevention Trial (PCPT) and Reduction by Dutasteride of Prostate Cancer Events (REDUCE), in which Finasteride and Dutasteride effect on cancerogenesis was assessed. According to results of the studies the role of 5-alphareductase inhibitors wasn't demonstrated [6]. It should be mentioned that design of those studies didn't include separate assessment of drugs effectiveness namely in patients with PIN [7]. But taking into consideration prostate cancerogenesis and mechanism of action of 5-alpha-reductase inhibitors, it could be promising to investigate Dutasteride effectiveness in patients with PIN as a precancerous process with malignization possibility without treatment [4].

Transurethral prostate resection (TURP) is a well known "gold standard" of surgical treatment of benign prostatic hyperplasia (BPH). During TURP is removed mostly central part of the prostate is, and in 2.8–33 % of cases PIN is detected after pathomorphology. To date in most cases subsequent story of these patients remains to be unclear because among physicians dominates the opinion that such precancerous states, PIN has little clinical significance. This is the reason of insufficient surveillance and lack of treatment.

Patients with diagnosed PIN are a risk group for malignant transformation and PC progression. For this reason, investigations of Dutasteride and TURP effectiveness are actual in the aspect of precancerous state malignization.

**The purpose** of the study was to investigate the effectiveness of 5-alpha-reductase inhibitor Dutasteride and transurethral prostate resection in the treatment of patients with prostate intraepithelial neoplasia of peripheral and central zones.

Materials and methods. The study included 130 patients with combined PIN of peripheral and central zones with age from 51 to 75 years (middle age 64.3±1.3 years), which were treated in mini-invasive centre of State institution of science "Research and practical center of preventive and clinical mmedicine" State administrative department from February 2009 till may 2014. All patients signed informed consent before taking part in the study. PIN was diagnosed through transrectal multifocal prostate biopsy, performed due to PC suspicion (high PSA level, sonography data, digital rectal examination). All patients were divided into 4 groups depending on treatment options. The first group of patients (n=32) had no special treatment and were under active surveillance. The second group (n=40) were treated with 5-alphareductase inhibitor Dutasteride 0.5 mg a day during 1 year. TURP was performed in the third group of patients (n=30). Patients of the fourth group (n=28) had combined treatment, TURP and Dutasteride 0.5 mg a day during 1 year. The follow-up period was 3 years, during which transrectal multifocal prostate biopsies under sonography control were performed with 6 months' interval. Rebiopsies were planned. Their aim was to assess morphological prostate tissue changes, PIN and adenocarcinoma detection. Besides, unplanned rebiopsies were performed on medical indications, such as changes of prostate palpation, higher PSA level (in this case taking into consideration that one of the Dutasteride effects is reduction of total PSA level in 50 %), suspicious data in editional examination methods (sonography, MRI).

Study results had statistical data processing using licensed software Statistica 6.0 StatSoft Inc., USA. According to sample size and value distribution were applied methods of nonparametric statistics (Mann-Whitney U test). Corellation between parameters was established using Spearmen correlation coefficient. The difference was considered credible with p<0.05.

**Results of the study and their discussion**. The treatment results of patients with combined PIN of peripheral and central zones were assessed through the rate of PIN malignant transformation, namely PC detection considering PC stages. Follow up period amounted to 3 years.

Aggregated data about rate of prostate adenocarcinoma detection in patients with PIN of peripheral and central zones indicate adenocarcinoma diagnosis in 36 patients which is 27.7 % from the general patients' number (130) who took part in the study.

Among patients of the first group were detected 22 (68.8 %) PC cases, among second group -6 (15 %) PC cases, among the third group -4 (13.3 %) cases and among the fourth group -4 (14.3 %). Therefore, statistically significant difference was determined in relation to PC detection rate in patients with combined PIN of peripheral and central zones between the patients of the first group and second group, third group and fourth group in 53.8 %, 55.5 % and 54.5 % respectively, (p<0.05), (Fig. 1).

Rebiopsy interval was 6 months. Analysis of time distribution of detected PC cases established that during the first year of follow up prostate adenocarcinoma was diagnosed in 4 patients, 11.1 % of general amount of detected PC.

During the second year of follow up PC was detected in 14 patients (38.9 %). During the third year of follow up period PC was diagnosed in 18 patients (50 %) as shown in Fig. 2.



Fig. 1. PC rate detected in studied groups of patients.

Fig. 2. PC rate in patients with PIN during 3 year follow-up period.

Year3

During first year follow-up PC rate in patients with PIN was statistically significantly less than during second and third years, namely by 27.8 % and 38.9 % respectively (p<0.05).

One of the research objectives was to assess stage distribution of detected PC cases in patients with PIN of peripheral and central zones during 3-year follow up period. It should be mentioned that among 36 patients in 12 (33.3 %) cases was diagnosed PC of the I stage, in 14 (38.9 %) patients – PC of the II stage, in 6 (16.7 %) cases – PC of the III stage and in 4 (10.1 %) patients was detected prostate adenocarcinoma with bone metastasis (Table 1).

Table 1

	1 1		1 v 8	
patients	PC stage I	PC stage II	PC stage III	PC stage IV
group 1	10	6	4	2
group 2	0	2	2	2
group 3	0	4	0	0
group 4	2	2	0	0
total	12 (33.3 %)	14 (38.9 %)	6(16.7%)	4 (10.1 %)

Distribution of detected PC cases in patients with PIN of peripheral and central zones by stages

Attention should be payed to distribution of patients with PC III-IV stages depending on treatment options. Comparative analysis of PC stages distribution between study groups showed that there were no PC III-IV stages among patients of the third and of the fourth groups. At the same time in 4 patients of the first group (active surveillance) was detected PC in the III stage and in 2 patients of the first group – PC in the IV stage, what amounted 9 % of diagnosed PC. 2 patients of the second group had PC in the III stage and in 2 patients of the second group was diagnosed PC in the stage IV.

Obtained data demonstrate the effectiveness of use of such treatment methods as 5-alpha-reductase inhibitor Dutasteride, surgery (TURP) and their combination in patients with combined PIN localization in peripheral and central zones of the prostate. In relation to comparative analysis of effectiveness of TURP, Dutasteride and combination TURP and Dutasteride should be mentioned that no statistically significant advantages of one of these methods were established in patients with PIN of peripheral and central zones. The rate of PC had no statistically significant differences between 2, 3 and 4 groups (P>0.05). Besides, patients with PIN of peripheral and central zones whom TURP was performed had lower risk of III and IV stages of prostate adenocarcinoma.

Today the database is accumulated and constantly updated, demonstrating the clinical significance of PIN as precancerous state. The problem of feasibility of special medication or surgical treatment of patients with PIN is controversial because of the opinion that clinical significance of this pathology is limited and is not dangerous for patients' life. At the same time according to data of our study absence of treatment causes malignization in 68.8 % of cases. In spite of REDUCE data, that didn't confirm Dutasteride role for PC prevention [4], and data of Milonas and coauthors, who didn't detect decrease in PC incidence in patients with high grade PIN after Dutasteride [10], our data demonstrate effectiveness of Dutasteride in patients with PIN. Obviously, the cause of disperancy is different including criteria. Dutasteride decreases the rate of malignant transformation namely in patients with PIN.

TURP is a "gold standard" of benign prostate hyperplasia (BPH). Postoperative histology with prostate hyperplasia and PIN combination is a subject of discussion in relation to further tactics [8]. TURP allows to remove central zone prostate tissue with PIN. After TURP PC rate decreased by 55.5 % during 3-year follow-up. Therefore, obtained results demonstrate clinically justified feasibility of active tactics in relations to patients with PIN. Operative treatment, namely TURP, is a method of removal of precancerous PIN peaces and a method of prostate adenocarcinoma prevention.

### Conclusions

1. Combined peripheral and central zones PIN is a precancerous pathological state, which progresses without treatment in 68.8 % of cases into PC during 3-year follow up period.

2. Rate of diagnosing PC in IV stage in patients with PIN of peripheral and central zones, who have no treatment amounts 9 %.

3. Treatment of patients with PIN of peripheral and central zones using Dutasteride decreases PC rate by 53.8 %, transurethral prostate resection decreases PC rate by 55.5 %, combined treatment using Dutasteride and TURP decreases PC rate by 54.5 %.

Prospects of further research. Based on performed studies it should be mentioned that patients with PIN represent heterogeneous group and have different morphological features. PIN grade (low or high), PIN localization (peripheral, central zone or their combination), spread in the prostate (one or several biopsy samples, one or both prostate lobes and immunohistochemical data characterize biological features of precancerous state and malignant progression probability.

Perspective task of further investigation is studying of correlation between mentioned factors and rate of malignant transformation, and detecting among patients with PIN the group of malignization risk. These patients need deep examination and determination of indications for special treatment.

#### References

1. Vilhova O. Suchasni pohlyady na histologichni osoblyvosti cholovichoyi statevoyi systemy World of Medicine and Biology. 2017;1(59):186–191]. [in Ukrainian]

2. Attard G, Parker C, Eeles R. Prostate cancer. Lancet. 2016; 387:70-82. doi.org/10.1016/S0140-6736(14)61947-4.

3. Bastarós J, Placer J, Celma A, Planas J, Morote J. Current significance of the finding of high grade prostatic intraepithelial neoplasia in the prostate biopsy. Actas Urol Esp. 2014 38(4); 270–5. doi: 10.1016/j.acuro.2013.10.001.

4. Bosland M. Is there a future for chemoprevention of prostate cancer. Cancer Prevention Research. 2016; 10:1940-6. doi: 10.1158/1940-6207.

5. Culp M, Soerjomataram I, Efstatiou J, Bray F, Jemal A. Recent global patterns in prostate cancer incidence and mortality rates. Eur Urol. 2019; 4: 2832–8. doi: 10.1016/j.eururo.2019.08.005.

6. Kang C, Xiangnan Li, Yabing Du, Xiance T, Seiji A, Yiwei G, Ying Xi. Chemoprevention of prostate cancer in men with highgrade prostatic intraepithelial neoplasia (HGPIN): a systematic review and adjusted indirect treatment comparison. Oncotarget. 2017; 8 (22): 36674–84. doi: 10.18632/oncotarget.16230.

7. Luis B, Amar SA, Holly S, Sakunthala K, Geraldine S, Henrik M, et al. Histopathologic False-positive Diagnoses of Prostate Cancer in the Age of Immunohistochemistry 1 3; Transatlantic Prostate Group. Am J Surg Pathol 2019 Mar;43(3):361–368. doi: 10.1097/PAS.000000000001202.

8. Milonas D, Auskalnis S, Skulcius G, Gudinaviciene I, Jievaltas M, Joniau S. Dutasteride for the prevention of prostate cancer in men with high-grade prostatic intraepithelial neoplasia: results of a phase III randomized open-label 3-year trial. World J Urol. 2017; 35:721–728. doi: 10.1007/s00345-016-1938-8

9. Mohanty P, Nanda A, Mohanty L.Indian J Histomorphological study of prostatic adenocarcinoma and its mimics. Pathol Microbiol. 2019; 62(2):251–260. doi: 10.4103/IJPM.IJPM\_322\_18.

10. Montironi R, Modena A, Ciccarese C, Iacovelli R, Brunelli M, Fiorentino M. Immune Checkpoint Inhibitors and Prostate Cancer: A New Frontier? Oncol Rev. 2016; 10:287–93. doi: 10.4081/oncol.2016.293.

11. Montironi R, Zhou M, Magi-Galuzzi C, Epstein J Features and prognostic significance of intraductal carcinoma of the prostate. Eur Urol Oncol. 2018; 1:21-8. doi: 10.1016/j.euo.2018.03.013.

12. Nakay Y, Tanaka N, Miyake M, Hori S, Tatsumi Y, Morizawa Y, et al. Atypical small acinar proliferation and two or more cores of high-grade intraepithelial neoplasia on a previous prostate biopsy are significant predictors of cancer during a transperineal template-guided saturation biopsy aimed at sampling one core for each 1 mL of prostate volume. Res Rep Urol. 2017; 21: 187–93. doi: 10.2147/RRU.S148424.

13. Patel P, Nayak J, Biljetina Z, Donelly B, Trpkov K. Prostate cancer after initial high-grade prostatic intraepithelial neoplasia and benign prostate biopsy. Can J Urol. 2015; 22 (6): 8056–62. PMID: 26688133.

14. Schwartzmann I, Celma A, Gallardo I, Moreno O, Regis L, Placer J, et al. In Search for risk predictors at the microscopic scenario of a negative biopsy. A systematic review. Actas Urol Esp. 2019; 43(7): 337–47. doi: 10.1016/j.acuro.2019.01.010.

15. Varghese J, Kuruvilla P, Mehta N, Rathore R, Babu M, Bansal D, et al. Incidentally Detected Adenocarcinoma Prostate in Transurethral Resection of Prostate Specimens: a Hospital Based Study from India. Asian Pac J Cander Prev. 2016; 17 (4):2255–8. doi:10.7314/apjcp.2016.17.4.2255.

Стаття надійшла 31.05.2022 р.