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Contemporary aspects of prostate cancer grading

Współczesne kryteria oceny złośliwości raka stercza

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Słowa kluczowe

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None
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S u m m a r y

Prostate cancer (PCa) incidence in Poland and many countries all over the world is second only to lung cancer incidence. Analysis of epidemiology data indicates a gradual increase in PCa incidence and mortality in recent decades, with the growth rate of mortality being smaller than the growth rate of incidence. Carcinogenesis is a complicated biological process and usually starts with mutation of normal cells to precancerous changes (atypical small acinar proliferation and prostatic intraepithelial neoplasia) and after that to carcinoma in situ and invasive cancer. Malignancy is defined according to rules devised by Donald Gleason. The "Gleason score" is a system that grades malignancy according to 5 Gleason patterns, with 1 being the least, and 5 being the most malignant. PCas are differentiated mainly by architecture and, to a lesser degree, neoplastic cell characteristics. Recently, a growing interest in magnetic resonance imaging application for predicting PCa malignancy has been observed.

S t r e s z c z e n i e

Rak gruczołu krokowego (ang. *prostate cancer* – PCa) zarówno pod względem rozpoznawalności, jak i śmiertelności jest jednym z najczęstszych nowotworów u mężczyzn w Polsce oraz w większości państw na świecie. Karcynogeneza w gruczole krokowym jest zjawiskiem złożonym biologicznie. Najczęściej rozpoczyna się od mutacji w komórkach nabłonka gruczołu krokowego i powstania zmian przednowotworowych: nowotworzenia śródnabłonkowego (PIN) oraz atypowego rozrostu drobnozrazikowego (ASAP). Doprowadza to do powstania zmian dysplastycznych o charakterze raka przedinwazyjnego (łac. *carcinoma in situ* – CIS), a następnie do powstanie raka inwazyjnego. Określenie stopnia złośliwości raka definiuje się według skali Gleasona, której istotą jest podział na 5 kategorii różniących się między sobą głównie architektoniką i – w mniejszym stopniu – wyglądem komórek nowotworowych. Obecnie coraz częściej w piśmiennictwie wspomina się o zastosowaniu badań obrazowych, w tym głównie rezonansu magnetycznego (MRI) w prognozowaniu złośliwości raka gruczołu krokowego.

Prostate carcinoma (PCa) is one of the most common cancers in men both in terms of incidence and mortality in Poland and worldwide (1).

Prostate cancer predominantly develops (70%) in the peripheral zone of the prostate gland. Approx. 10-15% of PCas are found in the transitional zone, and 15-20% in the central zone (2).

Carcinogenesis within the prostate gland is a biologically complex phenomenon. It typically begins with precancerous changes in the epithelium and progresses to invasive cancer. The processes commonly associated with precancerous changes or co-existing with cancer include prostatic intraepithelial neoplasia (PIN) and typical small acinar proliferation (ASAP). Originally, three PIN forms were recognized, differing by the degree of cellular abnormality and the percentage of abnormal epithelial cells: PIN 1 (benign), PIN 2 (moderate) and PIN 3 (severe) (3). Currently, just 2 PIN types

are differentiated, namely low grade and high grade (4). Low grade prostatic intraepithelial neoplasia (LGPIN) has been determined to differ in nature from high grade prostatic intraepithelial neoplasia (HGPIN), as it is associated with cancer only in isolated cases (5, 6), and does not constitute a separate pathomorphological entity (7). PIN is diagnosed based on multiple clearly defined architectural and cytological criteria (8). Several features make PIN a precancerous change. It occurs in the prostate in the fourth and fifth decade of life, and its prevalence grows with age. PIN precedes PCa by a minimum of 5-10 years (9). It is found in approx. 60-90% of PCas and is frequently situated near (< 2 mm) invasive cancer site (5, 9-12). As opposed to PCa, PIN retains an intact or fragmented basal cell layer, hence its presence is not associated with elevated PSA level in blood serum. The percentage of HGPIN found in needle prostate biopsy without coexisting PCa ranges from 0.15-16% (5, 13-20). Prevalence of PCa identified in repeat biopsy of a gland where previously HGPIN was found ranges from 22-100% (5, 6, 18-23).

Atypical small acinar proliferation (ASAP) is a pathological change of the prostatic epithelium that may be indicative of PCa. ASAP consists in the presence of foci of small, atypical glands suspicious for cancer, yet not referred to as cancerous, since their basal membrane is preserved (24). The percentage of ASAP diagnosed in needle biopsy of the prostate gland, without coexistence of cancer, ranges from 1.5-6.3% (5, 13-20), whereas the prevalence of PCa identified in a follow-up biopsy of a prostate gland where ASAP was previously detected ranges from 22-100% (5, 6, 18-23).

Owing to the different morphology of the changes listed above, it should be remembered that when a follow-up prostatic biopsy is conducted, the location of cancerous tissue may differ from the location of previously identified HGPIN, whereas every repeat prostatic biopsy of a gland where ASAP was previously identified should heavily focus on the areas where it was found (21, 23, 25, 26). The process of carcinogenesis (fig. 1) involves mutation of cells in the afore mentioned precancerous changes, which, in turn, leads to dysplastic changes resulting with carcinoma in situ (CIS), and ultimately with invasive carcinoma. The majority of prostatic cancers are multifocal. The multiple foci typically arise in various prostatic zones and are characterized by varying histological grades (27-29).

A crucial element of tissue core examination is identifying their malignancy score. Malignancy is defined according to the rules developed by Donald Gleason (1920-2008) that he originally described in 1966 in the journal "Cancer Chemotherapy Report", in his paper that had previously been rejected by two major urological journals (30-32). PCa grading according to Gleason scale is at present a universally used method of PCa evaluation.

As a young pathologist, Donald Gleason (fig. 2) worked on the histological interpretation of prostatic cancer at the Minneapolis Veterans Administration Medical Center from 1962. He based his study on the results of 280 prostatic biopsies performed between 1960-1964 (33). The scale he proposed has been in common use since 1978, when it was adopted by the American Cancer Society and approved by the WHO (33, 34).

Gleason scale recognizes 5 PCA malignancy patterns, ranging from 1 (least malignant) to 5 (most malignant) differing predominantly by the architectural features, and, to a lesser degree, by the appearance of the cancerous cells (fig. 3) (35).

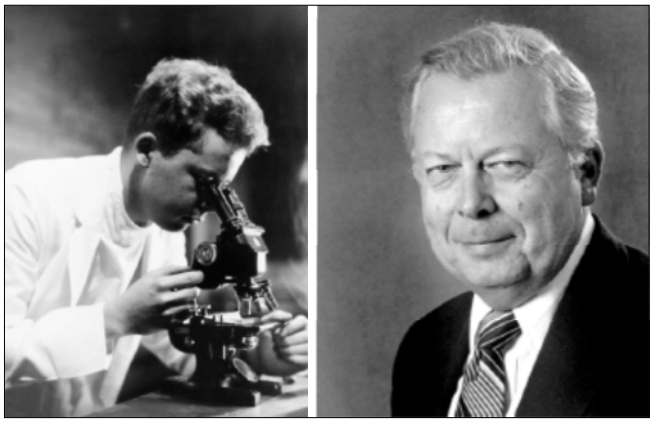

Fig. 2. Donald Gleason (34)

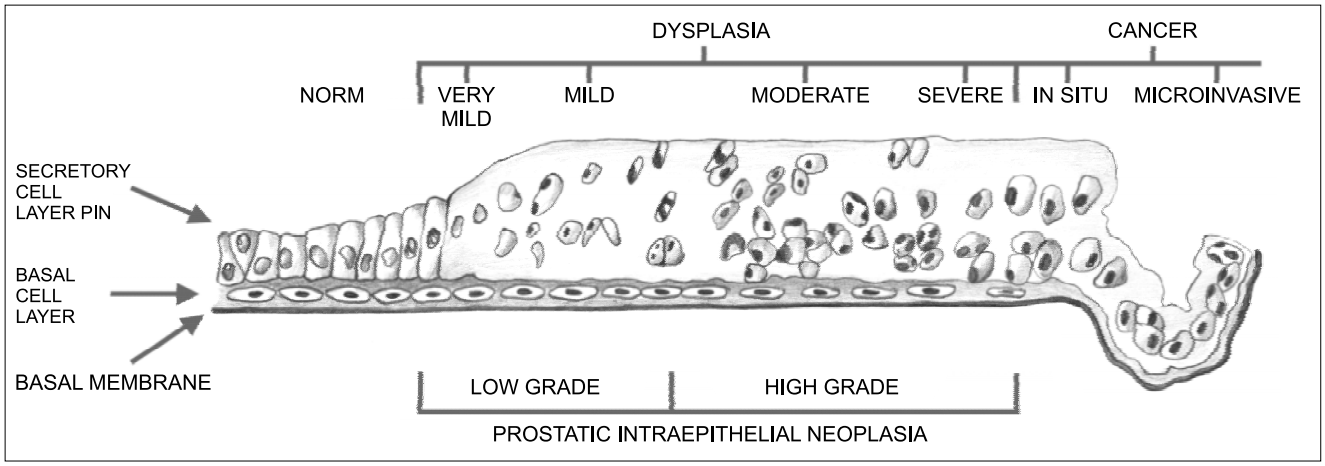

Fig. 1. Carcinogenesis of the prostate gland

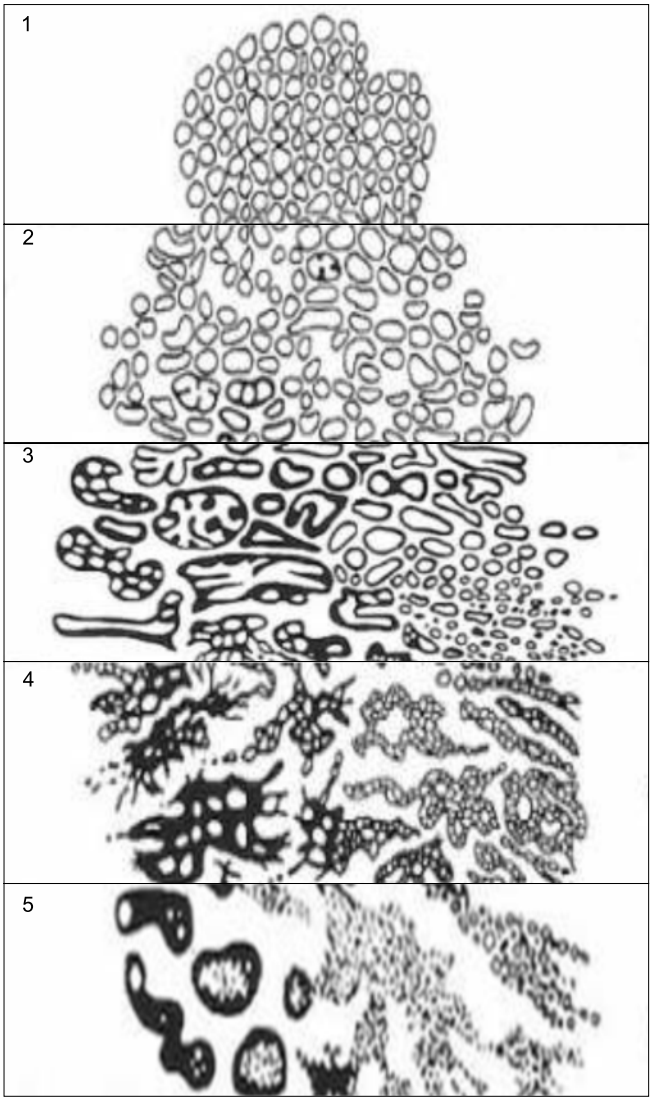

Fig. 3. 5 patterns of prostate cancer grading (35)

There are also other grading systems that are much less frequently used to assess the histological advancement of PCa, including systems by Mostofi, Böcking and Anderson (MDAH) (tab. 1). Mostofi scale identifies 3 degrees of glandular differentiation and nuclear anaplasia, as does Böcking scale. MDAH system comprises four grades and is based the percentage of tumor that forms the gland (35). See table below for the comparison of different systems of PCA grading.

Tab. 1. PCa grading systems

	Grade 1	Grade 2	Grade 3
Gleason score	2, 3, 4, 5	6, 7	8, 9, 10
Mostofi	1	2	3
Böcking	1	2	3
MDAH	1	2, 3	4

While assessing tumour grade in Gleason scale, the pathologist identifies the most common and the next-most common pattern in a given tumour, assigning each of them with a numerical value (1-5). The sum of those two numbers comprises Gleason score (Gl.s.) reflecting the global malignancy of the prostate cancer found in the gland, e.g. Gl.s. 5 = 3+ 2 (Gl.s. 7 = 4 + 3) means that the most common histological pattern identified by the pathologist in the tumour is 3, and the next-most common Gleason pattern is 2. If only one histological pattern is found, two identical numbers are added, or the number is multiplied by two (e.g. Gl.s. 6 = 3 + 3 or 3 x 2).

For PCa malignancy patterns see figures 4-10.

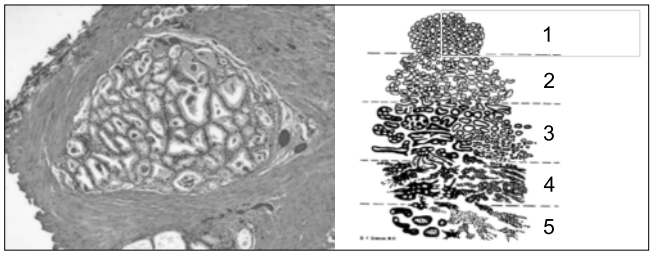

Fig. 4. Gl. pattern 1. A limited tumour with closely packed but still discrete, uniform, round or oval, middle-sized glands (larger than in pattern 3). Figures by courtesy of the Pathomorphology Division of the Centre of Postgraduate Medical Education in Warsaw, part of collection by Maciej Wysocki MD, PhD and Artur Bartczak MD, PhD

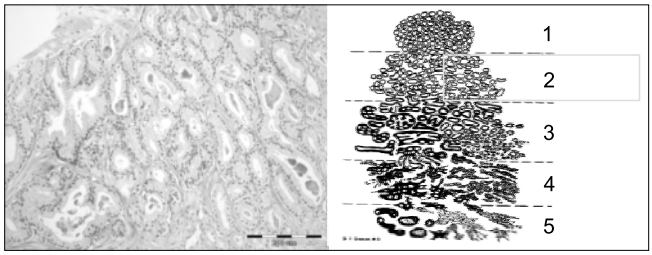

Fig. 5. Gl. pattern 2. Similarly to Gl. pattern 1, the margins of the tumour are fairly well- defined, yet may be minimally infiltrated; more space between glands, which are not as uniform as in pattern 1

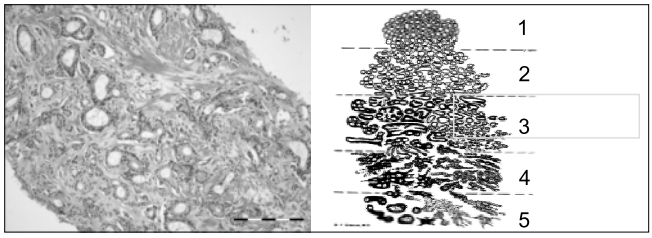

Fig. 6. Gleason pattern 3. Separate clusters of glands that are notably smaller than in Gl. pattern 1 and 2; infiltrates within and between non-neoplastic glands of the prostate. Clear differences in the size and shape of the glands. Poorly-formed, discrete, small cribriform glands

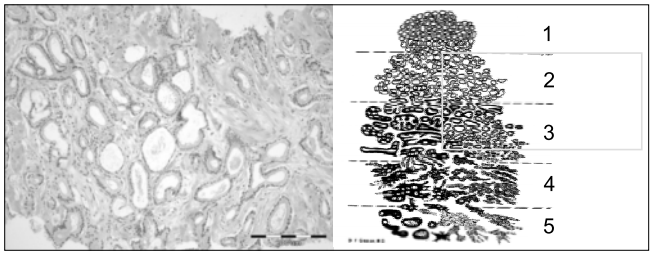

Fig. 7. Gl. score 5 (2 + 3)

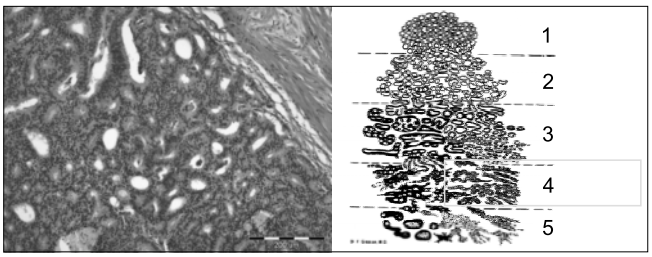

Fig. 8. Gleason pattern 4. Fused small irregular glands lacking glandular lumen; large cribriform glands and cribriform glands with poorly defined margins (sometimes similar in structure to adrenal glands)

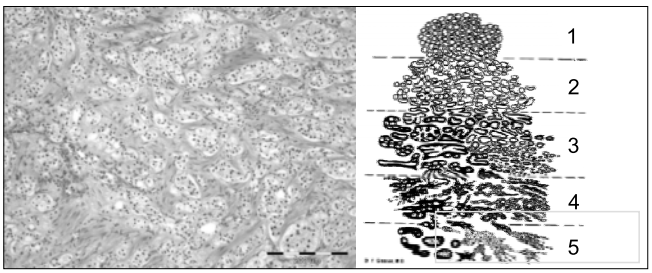

Fig. 9. Gleason pattern 5. Lack of glands; sheets of cells, cords, and single cells, comedocarcinoma with central necrosis surrounded by papillary, cribriform or solid structures

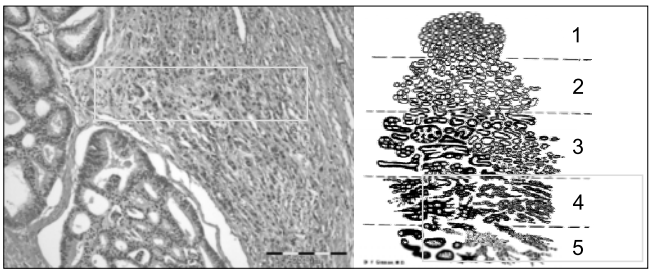

Fig. 10. Gl. score 9 (4 + 5)

The fairly complex Gleason system makes the evaluation quite subjective, which may in turn lead to discrepancies in malignancy grades when the same tissue samples have been examined by two different urologic pathologists (inter-observer variability) or even by the same pathologist at different times (intra-observer variability) (36-47).

In 2005, new standards for the evaluation of histopathological prostatic material were assumed at a consensus conference of International Society of Urological Pathology (ISUP) (48, 49).

As a result, the following guidelines for PCa diagnosis were published:

1. Gl.s. 2 (1 + 1) based on tissue core samples or surgical specimens should not be diagnosed.
2. The diagnosis of Gleason scores 2 through 4 based on tissue core samples should not be reported.
3. For cancers of high malignancy reflected by the first Gleason number ($Gl.n_1$) = 4 or 5, the second Gleason number should be ignored if it reflects lower malignancy and is identified in tissue material comprising < 5% of total PCa volume,
4. If areas of high-grade cancer (Gl.n. ≥ 4) are not most (primary) or next-most frequent (secondary) patterns, they should still be registered as the second Gleason number.
5. If Gleason number appears moderate (Gl.n. 3) it should be recognized and registered as Gl.n. 4 (which will in most cases cause Gl.s. 6 shift to Gl.s. 7).
6. Ductal adenocarcinoma should be graded as Gl.s. 8 (4 + 4).

A study published 3 years after ISUP guidelines were released (50) evaluated their effect on PCa grading. The pathologist who had examined tissue core samples back in 1997-2003, re-assessed 172 of them in 2008: the percentage of concordant $Gl.n_1$, $Gl.n_2$ and Gl.s. was 83.1, 63.3 and 68% respectively. The discrepancies in grading changed PCa risk group for 29.1%, with 26.7% of the samples having been previously undergraded, and as little as 2.3% overgraded.

Recently, studies discussing the application of imaging examinations, particularly MRI, in the grading of PCa (51) have been increasingly common. Endorectal coil (ERC) has been used for the morphological evaluation of the prostate gland, and prostate imaging with this modality was up until recently believed the most accurate method (52). As technological progress brought about 3.0 T mpMRI, no evident difference was found in the results of the two modalities, resulting in a greater popularity and wider application of MR for prostate gland imaging. MRI is especially effective in identifying cancer foci located in the frontal portion of the prostate gland, where biopsy is very difficult to perform (54, 55). MR images can help detect high grade and low grade cancer (51). Also, MRI has been demonstrated to be a very efficient tool for identifying high Gleason score PCa (> 7) (56, 57). In 2014, another ISUP meeting took place, revising and revolutionizing the previously used system of PCa grading. (58). With the fairly complex Gleason system and the resulting score discrepancies in mind, the objective was to simplify it. 5 PCa categories were developed, from the least to most malignant. Groups 1, 4 and 5 cover 3 previous categories each. Table 2 below shows both the old and the new system of PCa grading. ISUP recommended that both systems be used in the years 2014 through 2016. Nonetheless, it is in fact the experience and the conscientiousness of the examining pathologist that remains of paramount importance in PCa grading.

Tab. 2. The new and the previous system of PCa grading

New ISUP Grading System for Prostate Cancer	
2005 Modified Gleason Grading	**2015 ISUP Grade**
3 + 3, 3 + 2, 2 + 3, 2 + 2	1
3 + 4	2
4 + 3	3
4 + 4, 3 + 5, 5 + 3	4
4 + 5, 5 + 4, 5 + 5	5

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