Extended abstract
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The role of pathologist in diagnosing and treatment of prostatic cancer

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Excluding the skin cancer, prostatic carcinoma is the most common malignant neoplasm of men. Its incidence is increasing, but it is not quite clear whether this increase is genuine or is caused by a higher rate of diagnosing due to an inexpensive laboratory analysis of the serum level of prostate specific antigen (PSA), and a relatively simple needle core biopsy technique by which the majority of the prostate carcinomas are detected. The role of pathologist in diagnosing and treatment of prostatic carcinoma is dual. In the first stage, the pathologist is responsible for an accurate diagnosis of carcinoma and provisional estimation of the tumour's differentiation (grading), and other prognostically significant morphological characteristics in the tissue obtained by a needle core biopsy or, less often, by a transurethral resection of prostate (TURP). In the second stage, in the tissue obtained by radical prostatectomy, the pathologist makes a final diagnosis, including a final, precise grading and assessment of the factors important for staging of disease. There is a fairly good correlation between the tumour grade and behaviour, and a combination of the tumour's grade and clinical stage of disease provides an even better tool for prediction of prognosis. Even though the tumour grade and stage of disease are usually in agreement i.e. poorly differentiated carcinomas are most commonly in an advanced stage at the time of diagnosis, there are exemptions of that rule. The importance of perineural invasion within the prostate is not quite clear. On one side are the authors who present a "firm" proof of its significance for prediction of bone metastases and/or an early recurrence after surgery. However, there is an equally strong evidence against its significance as an independent prognostic factor. Prostatic carcinoma spreads via pelvic lymphatics into the lymph nodes around internal and common iliac arteries and aorta. Usually only obturator lymph nodes are received, either for frozen-section diagnosing or as a part of surgical specimen. However, there are some data according to which absence of metastases in these lymph nodes is not an absolute indication of non-existence of lymphogenous metastases as in some large series metastatic deposits were relatively frequently found only in the iliac lymph nodes. Hematogenous propagation is, usually, a relatively late event, with the tumour cells spreading through the pelvic veins and inferior vena cava and resulting in systemic dissemination. The most common hematogenous metastases are in the bones of vertebral column and pelvis, and, opposite to the other tumours' bone metastases, these are generally osteoblastic. Correct handling of the tissue obtained either by biopsy or by TURP or radical surgery is of the great importance. The material obtained by a needle core biopsy usually consists of six or more cores and fragments of tissue, measuring up to 20mm in length and less than 1mm in diameter. The pathologist should register the total number of cores and their length and, if possible put them in the cassettes stretched, in the single plane, avoiding crowding and overlapping. All the paraffin blocks should be routinely cut at six different levels and stained by haematoxylin and eosin (H&E). Occasionally, in the cases when the differential diagnosis comprises prostatic intraepithelial neoplasia (PIN), cribriform hyperplasia, and/or large duct papillary and cribriform carcinoma, antibodies against PSA and high molecular weight cytokeratin (HMWCK) can be used. In the final report, the exact number (%) of the cores involved by the tumour should be stated as this plays an important role in the assessment of the stage of disease and prediction of the early recurrence after prostatectomy. Presence or absence of PIN should always be recorded, particularly in the cases where no invasive carcinoma is found as its existence indicates a possibility of nearby invasive carcinoma and results in a very close follow-up of the serum PSA and a repeat biopsy. In addition, it is important to register presence or absence of vascular space invasion and, despite its unsolved significance, perineural invasion. The tissue obtained by TURP should be weighed and first 12g completely processed in six cassettes. Of the remaining tissue approximately 2g (one cassette) per each 5g should be taken. If the specimen is too scanty, cutting of the block at least at three different levels is recommended. The specimen obtained by radical prostatectomy (prostate, seminal vesicles, and proximal portions of both vasa deferentia) should be weighed and the dimensions of prostate, seminal vesicles and stumps of both vasa deferentia should be measured. Overnight fixation in an adequate amount of neutral buffered formalin, and painting of each half of the prostate with a different dye is recommended. If needed, tissue for molecular genetic examination can be taken "fresh", before fixation, with a thick needle ("trucut") or by knife. Trimming of the prostate starts by shaving of 3 - 4mm thick slices from the apex and base, serial cutting of those perpendicularly to the resection margin, and processing of all the sections in an adequate number of standard blocks. The rest of the prostate should be serially cut, starting from the apex towards the base, parallel to the plane of the first apical section (perpendicularly to the urethra), with each section measuring 3 - 5mm in thickness. Both neuro-vascular pedicles should be included in some of the sections. The last section through the prostate should be at the level of seminal vesicles' attachment and should include their bases. This is very important because a prognostically significant invasion into the seminal vesicles is usually seen at this level. Finally, the rest of the seminal vesicles should be cut longitudinally, from the apex towards the base, and embedded together with the section taken from the resection margin of the corresponding vas defferens. If it is not possible to process sections by a "macroblock" technique, each section of the prostate can be cut in three ("Mercedes Benz sign" with the point of section on the utriculus) or four pieces (two from each half), with a precise marking of location. The most accepted method of grading of prostate carcinoma is based on assessment of the Gleason's morphological pattern, or, in fact, on the sum of the two commonest tumour patterns in any particular tumour. Gleason originally described five different patterns and labeled them by the numbers 1 - 5, with the pattern 1 being the best differentiated and pattern 5 practically completely undifferentiated. Actually, this system is based on estimation of the capability of the tumour cells to organize in the pattern that resemble normal prostatic tissue. Gleason's score results from adding the two largest tumour components, regardless of their particular grade of differentiation, with the first number belonging to the largest and the second number to the second largest component (e.g.. 3 + 4 = 7). If the tumour shows a single architectural pattern, this number should be doubled (e.g.. 3 + 3 = 6). The total sum obtained in this way can range from 2 to 10,

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with the tumours with the Gleason's score 2 - 4 being well differentiated (G I), those with the score 5 - 7, which are the most common, moderately differentiated (G II), and those with the score 8 - 10 are poorly differentiated (G III). If there is a third, less well differentiated pattern, the score is still made by adding the two largest components, but presence of the third, poorly differentiated one, should be reported. This is particularly important in the biopsy specimens as they may not be absolutely representative of the large tumour. Actually, it has been shown that assessment of the Gleason score in the biopsy specimen underestimates the real tumour differentiation in up to 30% of the cases, compared to the tissue obtained by radical prostatectomy. Gleason patterns 1 and 2 very much resemble a normal prostate and are diagnosed pretty rarely, particularly in the biopsy material. They are both composed of simple, round, small to medium sized acini. In the pattern 1 they are closely packed in well circumscribed, rounded masses, with minimal if any stromal invasion. In the pattern 2, the acini show some variation in shape and are loosely packed in rounded masses, which are less well circumscribed, showing a mild stromal invasion. The acini in both these patterns are lined by a single layer of epithelial cells (basal cells are missing), similar to a benign epithelium, with a relatively abundant eosinophilic or pale amphophilic cytoplasm, and regular, round or oval nuclei with conspicuous nucleoli. Gleason pattern 3 is by large the most commonly diagnosed pattern and, on its own, together with the patterns 1 and 2 is regarded as a well differentiated tumour. This pattern also resembles a normal prostatic tissue and is made up of variably packed, irregular masses of either small or medium sized to large acini, which are angular and show variation in shape. There is an obvious stromal invasion with infiltrative peripheral borders. The acini may contain an eosinophilic or basophilic secretion and/or crystalloid structures. They are also lined by a single layer of epithelial cells, the cytoplasm of which is more basophilic than in the patterns 1 and 2. Gleason pattern 4 exhibits a distorted or completely lost glandular architecture. This pattern, instead, shows a microacinar, papillary and/or cribriform appearance, with small acini fused in chains and cords, with a marked stromal invasion and raggedly infiltrative peripheral borders. The cells in this pattern usually have a dark cytoplasm but there is a variant with a clear cytoplasm ("hypernephroid" appearance), resembling a classical renal cell carcinoma. In the Gleason pattern 5 glandular lumina are difficult to find, and only occasional incompletely formed acini can be seen. These tumours are made up of fused sheets and masses of obviously malignant cells and show a marked stromal invasion with raggedly infiltrative margins. They are often called undifferentiated carcinomas and, together with a pattern 4 form a group of tumours with poor prognosis. These tumours are, fortunately, pretty rare and are exceptionally diagnosed in the early stage of disease. In addition to making a diagnosis, it is important to investigate a potential extraprostatic spread (ES) of carcinoma i.e. expansion of carcinoma through the prostatic "capsule". "Capsule" is not a well defined anatomic structure but represents a condensed layer of peripheral parenchyma, containing a variable amount of smooth muscle and collagen fibres and measures between 0.5 - 2mm in thickness. It is poorly developed or absent in the regions of apex, base and anteriorly. Therefore, evaluation of ES in those regions is restricted to identification of presence or absence of the tumour at the margins of resection. Key criteria for definite ES are: presence of malignant cells in adipose tissue (there is no adipose tissue in the prostate!), perineural invasion in the neuro-vascular "pedicles" (on the postero-lateral sides of prostate - 5 and 7 o'clock in the transverse sections), tumour surrounding ganglion cells (there are no ganglion cells within prostate), carcinoma within the striated muscle on the anterior side of prostate at some distance from the ill defined zone of bordering with the prostatic fibro-muscular stroma (rare event in the large tumours that arise in the "transitional" zone of prostate). ES is found in 23 - 52% of radical prostatectomy specimens. There is a statistically significant correlation between the tumour volume and ES - ES is found in only 2% of the tumours smaller than 0.46ml, but in as much as 52% of the large tumours. Clinical importance of ES lies in a significantly less favorable prognosis of these tumours compared with the prostate confined carcinomas. One of the pathologists' tasks is estimation of completeness of resection by search for presence or absence of the tumour cells at the painted margins of the specimen. It is very important not to misinterpret positive margins as ES, particularly in the cases in which the surgeon has cut into the prostate. In those cases the tumour can still be prostate confined but it should be recorded that it is not specimen confined, indicating an incomplete resection. If the extraprostatic tissue is lacking in the specimen, than the surgical margin of resection is either at the surface of prostate itself or within the capsule or in the prostate, if the cut has gone through them. Presence of the tumour on such a margin is better to be regarded as T2+ than as T3 stage, but ES can be neither confirmed nor excluded. Positive margins of resection are found in 33 - 37% of cases and show a significant correlation with the tumour volume and number of involved cores in the original biopsy specimen. It has been generally accepted that the positive margins in the tumours with the volume of less than 4ml are jatrogenic. The tumour is most commonly present at the margin in the region of apex (48%) and on the rectal and lateral surfaces (24%), but much less often at the basis/bladder neck (16%) and upper neuro-vascular pedicles (10%). The main significance of investigation of the resection margins lies in the fact that the probability of cancer related death is 60% in patients with positive margins while it is only 30% in patients with specimen confined carcinomas. Pathologist must be aware of "special" variants of carcinoma as well as the other malignant neoplasms of prostate as this, in some cases, can have significant consequences regarding treatment and prognosis of disease. The most common of "variants" is a so-called ductal ("endometrioid") adenocarcinoma which arises in the large periurethral prostatic ducts and shows a florid papillary, cribriform and/or solid epithelial proliferation. The biggest problem is in differentiating this tumour from the cribriform PIN, and absence of basal cells is of the greatest help. These tumours can belong to the Gleason pattern 3 (round to elongated masses of papillary and cribriform structures, with a variable size of glands, which, despite smooth and rounded peripheral borders, show a marked stromal invasion but mostly in an expansile manner); Gleason pattern 4 (solid, irregular masses of large cells with slit-like spaces and obviously infiltrative, ragged peripheral borders); or Gleason pattern 5 (any of the previous two associated with comedo-type necrosis). However, even when they are of the Gleason pattern 3, these tumours behave more like classical pattern 4 cancers, often associated with a relatively low level of serum PSA and earlier Hematogenous metastases in distant organs, including lungs. Small cell, undifferentiated carcinoma (neuroendocrine carcinoma of high malignant potential) is morphologically identical to the tumours of the same type in other organs, and, similarly, has a very poor prognosis with a mean survival of less than two years after diagnosis. These tumours can be associated with paraneoplastic syndromes (Cushing's syndrome, abnormal secretion of ADH etc.). The diagnosis of mucinous ("colloidal") carcinoma can be made only if at least 25% of the tumour contains extracellular mucus. Occasionally they resemble a colorectal adenocarcinoma and require an immunohistochemical investigation. Stage for stage, prognosis is similar or somewhat worse than in classical prostatic carcinoma. Signet ring-cell carcinoma has the same microscopic appearance as its counterpart in the other organs, especially in stomach, but the cells show a positive immunohistochemical reaction with the antibodies against PSA and prostate specific acid phosphatase (PSAP). It is usually associated with a classic adenocarcinoma in which case its prognostic significance is not clear. However, as a "pure" variant it has a very poor prognosis. Squamous cell carcinoma represents only about 0.5% of all primary tumours of prostate and its origin is not quite clear. It is often seen after hormonal or radiation therapy of classic adenocarcinoma and usually is associated with a normal level of serum PSA and PSAP, even in the cases with widespread metastases. However, the tumour cells can show a positive immunohistochemical reaction with the antibodies against these antigens. Opposite to the classic adenocarcinoma, bone metastases of the prostatic squamous cell carcinoma are usually osteolytic. To make a diagnosis of this tumour, presence of other primary carcinoma elsewhere in the body should be excluded, the tumour cells must have malignant characteris-

tics and invasive pattern of growth, and they must show squamous differentiation - keratin "pearls" and/or intercellular bridges as well as absence of glandular formation. However, the squamous component is most commonly associated with a classic adenocarcinoma resulting in a so-called adenosquamous carcinoma. Another rare tumour is a sarcomatoid ("spindle cell") carcinoma, usually associated with a typical acinar pattern, and its cells may show a positive reaction with the antibodies against cytokeratin (CK), PSA and PSAP. Prognosis is very poor, with a certain death in less than 48 months after diagnosis. Carcinosarcoma is another rare variant of prostate cancer with a similar prognosis as the previous one, and is composed of mixed classic adenocarcinoma and variable sarcomatous elements e.g. chondrosarcoma, osteosarcoma, leiomyosarcoma etc. Transitional cell carcinoma in the prostate is usually secondary, originating in the bladder, but can also arise as a primary in the prostatic urethra and/or large excretory ducts of prostate. It can exist as an in-situ and invasive tumour and by Pagetoid spread can involve ejaculatory ducts and seminal vesicles. Prognosis is poor and the main difference from the classic adenocarcinoma is that these tumours are refractory to anti-androgen therapy. Immunohistochemistry is of help in dubious cases (PSA, HMWCK, Thrombomodulin). Adenoid tumour of basal cells ("adenoid-cystic carcinoma"; "basal cell carcinoma") is, if it exists as a malignant neoplasm, extremely rare and is composed of nests of basaloid, round or oval cells, often with a cribriform architecture, intraluminal mucus and basement membrane-like material. So far, no cases with metastases or cancer related death are reported. Lymphoepithelioma-like carcinoma is also a very rare tumour composed of islands of tightly packed glands in a lymphocyte-rich stroma. A real prognostic significance of this tumour pattern is not known. Adenocarcinoma after anti-androgen therapy exhibits tightly packed, small, shrunken acini, but the cells have an abundant, clear cytoplasm and relatively large, hyperchromatic nuclei with inconspicuous nucleoli.

CONCLUSION

The role of pathologist in diagnosing and treatment of prostatic carcinoma is, maybe, more significant than for malignant tumours of some other organs. Reason for this is that clinicians, relying only on the results of laboratory and radiological investigation, can only make an educated guess whether the tumour exists, and of which type, grade and stage it is, and those are exactly the features on which further treatment and prognosis depends. Because of that, any prostatic tissue specimen, whether it is obtained by a needle core biopsy, transurethral resection or radical prostatectomy, should be handled with a greatest seriousness and complete awareness of all the aspects of this disease even though it requires a lot of time, resources, energy and, above all, knowledge, because the final result is of unmeasurable signifacance for the patient.

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