Histopathology of the Tumors

Giancarlo Troncone and Elena Vigliar

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Learning Objectives

By the end of the chapter, the reader will

- Be familiar with the basic concepts of histopathology of tumors
- Be able to recognize the hallmarks of malignant tumors
- Be able to integrate acquired knowledge into clinical practice

3.1 Definition

Neoplasia is an abnormal and uncontrolled cell growth; a mass of tissue that derives from this uncontrolled growth is termed *neoplasm* or *tumor* [1]. *Cancer* is the term commonly used to indicate malignant neoplasms, and the origin of the word dates back to the fourth century BC, when Hippocrates used the terms "carcinos" and "carcinoma" to describe non-ulcer-forming and ulcer-forming tumors [2]. *Cancer* comes from the Greek and Latin words referring to crab, because the swollen veins or the spreading projections from a malignant neoplasm looked like the limbs of a crab. The ability to invade adjacent tissues or spread to distant sites is, in fact, the leading feature that differentiates malignant from benign tumor. Generally, the terms *benign* and *malignant* refer to the clinical and biological behavior of a neoplasm as well as some specific morphological features. However, morphology does not always correlate with clinical course, i.e., *meningiomas*, benign tumors of meninges, may have malignant presentations and be lethal, depending on the size and location. Conversely *basal cell carcinoma*, a malignant skin tumor, is slow growing and locally aggressive but rarely metastasizes.

Benign and malignant tumor can be differentiated according to some main morphological features:

- Differentiation
- Modality of growth
- Rate of growth
- Metastasis

Differentiation describes the processes by which immature cells become mature, with specific functions [1]. As far as tumor cells, the term refers to how much the neoplastic population resembles the normal tissue: benign neoplasms are usually well-differentiated, whereas malignant neoplasm can range from well- to poorly differentiated.

3.2 Benign Neoplasms

The distinctive features of benign neoplasm are the lack of invasion of the surrounding tissues and the absence of metastases. As far as the modalities of growth are concerned, they have an expansive growth pattern in parenchymatous organs and an exophytic growth in hollow organs (Fig. 3.1). The formation of a connective tissue capsule may be observed, as a consequence of the compression atrophy of surrounding normal tissues (Fig. 3.2). Benign neoplasms are well-differentiated and closely resembling the corresponding cells of normal tissue they derive from; they have generally a slow growth rate, with a low number of mitosis (Table 3.1).

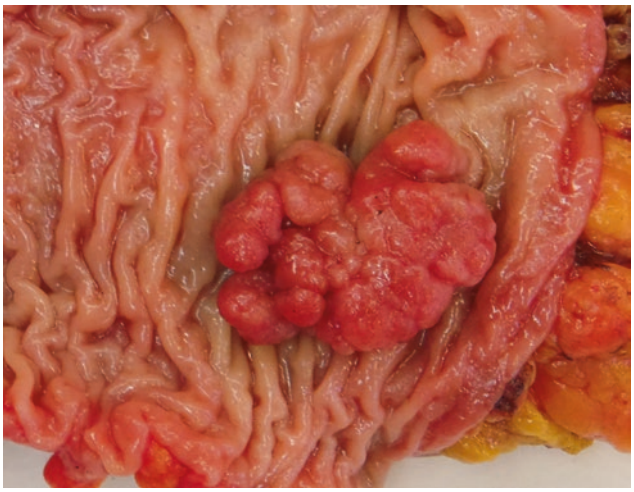

Fig. 3.1 Example of benign exophytic growth in hollow organs: adenomatous colonic polyp

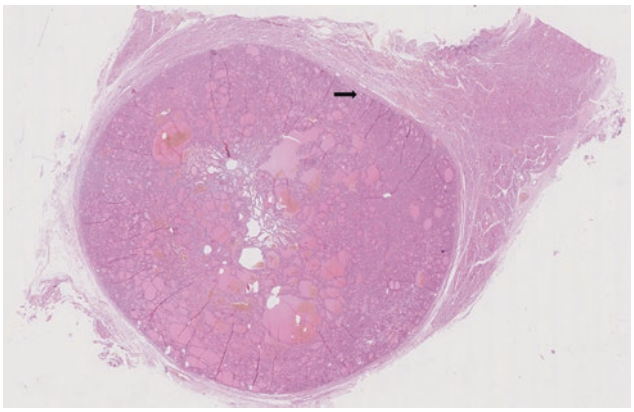

Fig. 3.2 Follicular adenoma of the thyroid: the benign neoplastic nodule is demarcated from the adjacent parenchyma by a thin, intact fibrous capsule

3.3 Malignant Neoplasms

Malignant neoplasms have the capability to invade and destroy surrounding tissue and metastasize to distant tissues [3, 4]. The diagnosis of malignancy is based on the assessment of various histopathological hallmarks (Table 3.1).

Modality of growth: The growth is usually chaotic and disorganized, with loss of polarity of tumor cells compared to the organization of the normal tissue of origin. The growth is characterized by the tendency to tissue invasion, with an infiltrative growth pattern in parenchymatous organs (Fig. 3.3); in hollow organs malignant neoplasms have the appearance of infiltrative plaques or ulcerative lesions (Fig. 3.4). Blood vessels are an essential component of neoplastic tissue, as they provide metabolic means and routes for metastatic expansion; tumor vessels tend to form tortuous networks with irregular branching patterns [5]. If neoplastic expansion is massive and fast, blood supply may be insufficient and central areas may undergo ischemic necrosis (Fig. 3.5).

Differentiation: Lack of differentiation is a distinctive feature of malignant neoplasms that can range from well- to moderately and poorly differentiated; undifferentiated tumors are defined "anaplastic" (anaplasia = loss of differentiation). *Pleomorphism* is a distinguish feature of lack of differentiation that consists in variation of shape and size of both cells and nuclei; *anisonucleosis* is the specific term to indicate the nuclei shape and size variation (Fig. 3.6).

Characteristically, nuclear size is increased but undifferentiated malignant cells may have a small appearance (i.e., malignant small round cell tumors) [6]; however, in both cases nuclear-cytoplasmic ratio (N-C ratio) is increased. Marked pleomorphism can

Table 3.1 Histopathological features of benign and malignant tumors

Feature	Benign	Malignant
Differentiation	Well-differentiated	Well- to poorly differentiated
Growth pattern	Expansive	Infiltrative
Growth rate	Slow	Rapid
Invasion	Absent	Present
Metastasis	Absent	Present
Necrosis	Absent	Present
Pleomorphism	Usually absent	Often present
Anisonucleosis	Absent	Often present
Nuclear-cytoplasmic ratio	Normal	Increased
Hyperchromasia	Absent	Often present
Nucleoli	Not prominent	Prominent
Mitosis	Rare	Increased, atypical

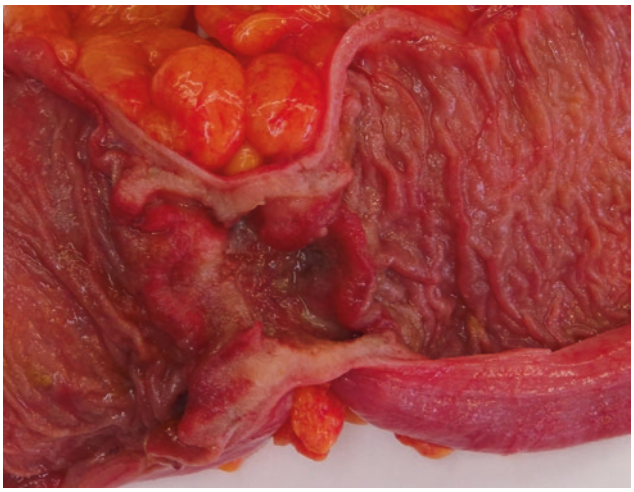

Fig. 3.4 Colorectal adenocarcinomas may have the appearance of infiltrative, ulcerated plaque

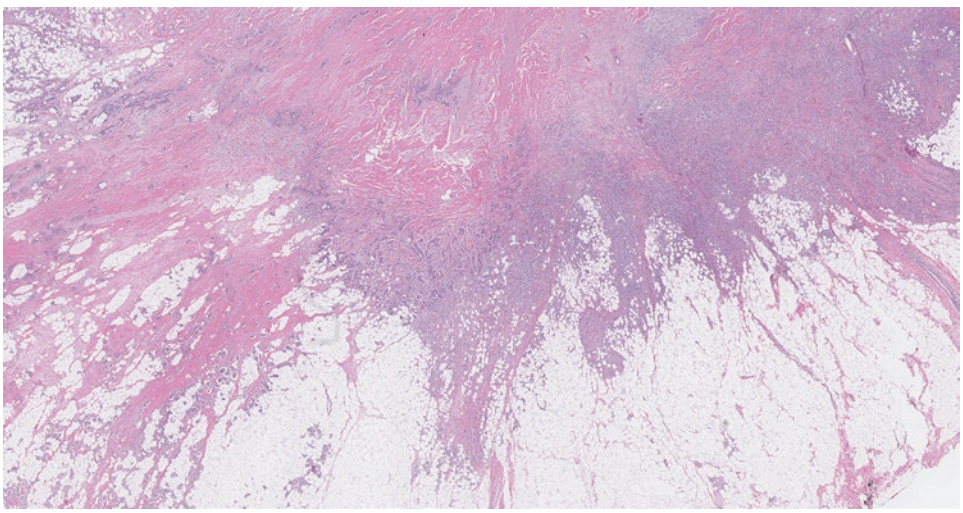

Fig. 3.3 Breast carcinoma: the growth of malignant tumor is characterized by the tendency to tissue invasion, with an infiltrative growth pattern in parenchymatous organs. Note the infiltration into breast adipose tissue

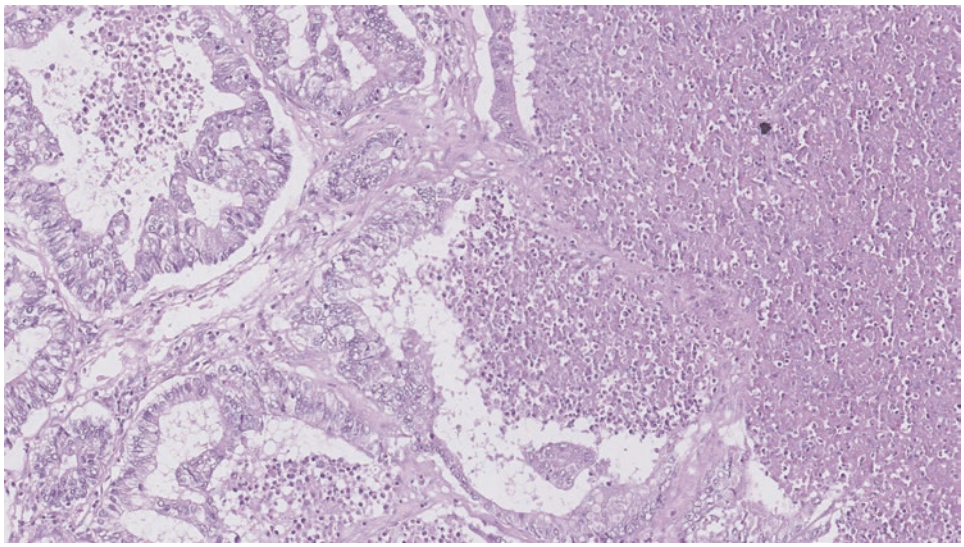

Fig. 3.5 Insufficient blood supply may cause ischemic necrosis of neoplastic central areas: a malignant neoplasm with a glandular growth pattern (on the left) and a large necrotic area (on the right)

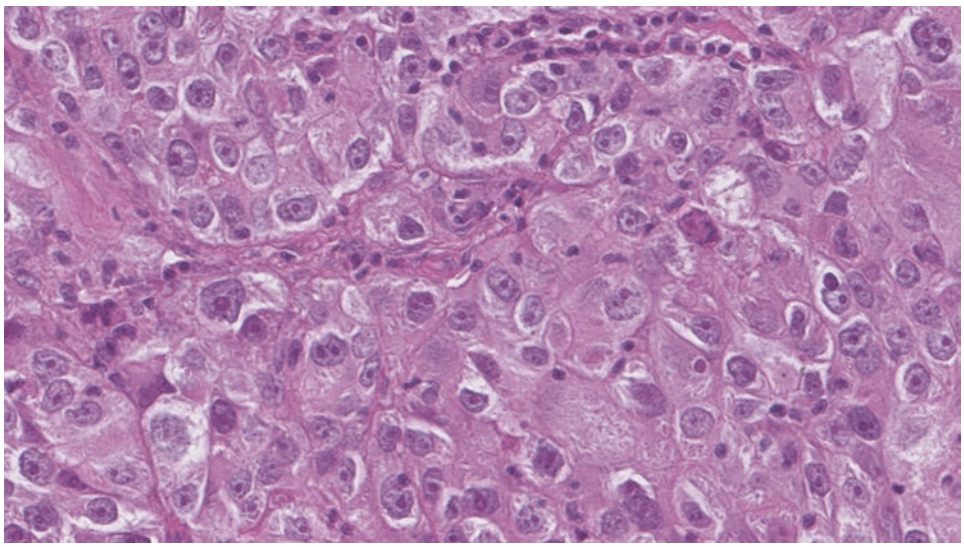

Fig. 3.6 Pleomorphism and anisonucleosis in a malignant tumor: note the variation of shape and size of cells and nuclei

lead anaplastic cells to assume the appearance of tumor giant cells, featured by the presence of a single, huge nucleus or multiple, bizarre nuclei (Fig. 3.7). Nuclear morphology is altered even with regard to nuclear chromasy: increased nuclear DNA content, resulting in a dark staining on hematoxylin and eosin (H&E) slides, is termed hyperchromasia. Otherwise chromatin may be coarse and clumped and distributed along the nuclear membrane (Fig. 3.8). Prominent, single or multiple nucleoli are usually present in malignant cells. Some types of cancer have hallmark nuclear alterations, i.e., papillary thyroid carcinoma (PTC) shows pale nuclei with powdery chromatin ("Orphan Annie" nuclei) and longitudinal nuclear grooves and intranuclear cytoplasmic inclusion, both expressions of the membrane irregularity (Fig. 3.9).

Mitotic activity: A high mitotic rate is a common feature of benign and malignant tumors, but also of hyperplasia, and reflects the higher proliferative activity of a cell population. Instead, the presence of atypical mitosis is a hallmark of malignancy. Normally, mitotic cell division occurs in a bipolar manner; however, in cancer cells, an excessive number of centrosomes may cause creation of supernumerary spindle poles [7, 8], which can result in multipolar mitosis (tripolar, quadripolar, bizarre mitotic figures) (Figs. 3.10 and 3.11). In several cancer types, the tumor mitotic rate is a significant independent prognostic factor (i.e., melanoma, neuroendocrine tumors) [9, 10].

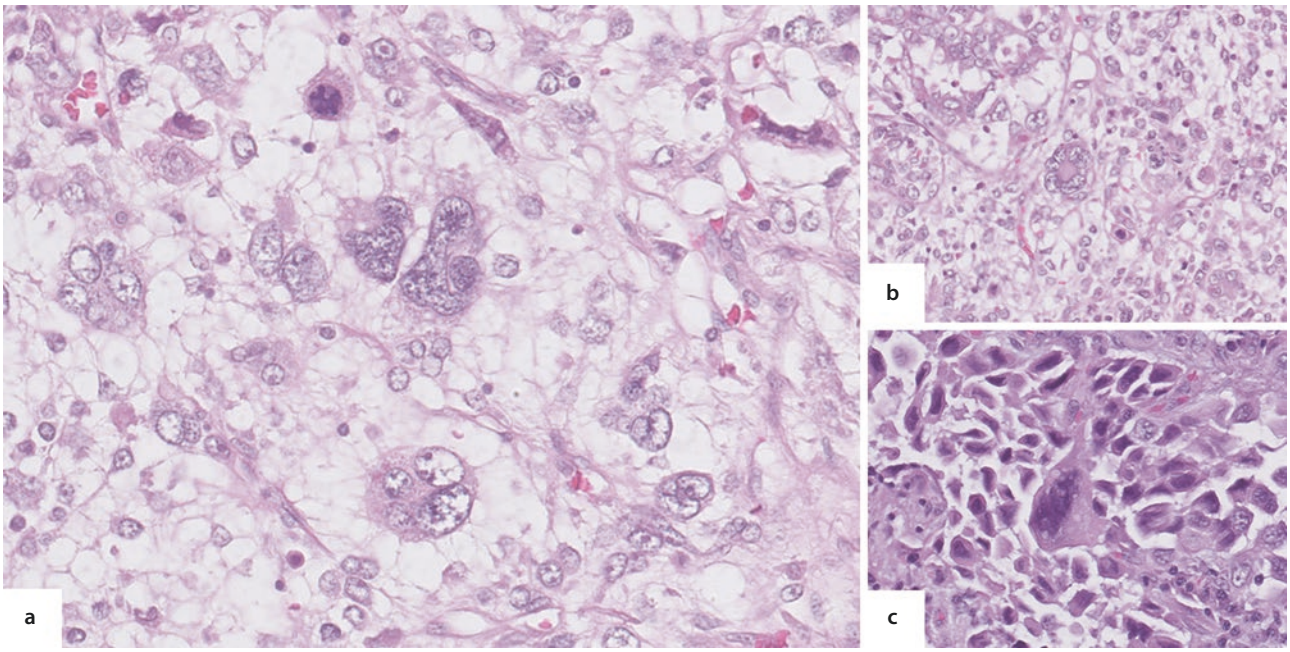

Fig. 3.7 Anaplastic tumor: malignant cells may assume the appearance of bizarre giant cells **a**. Tumor giant cells can be characterized by presence of multiple nuclei **b** or a single huge nucleus **c**

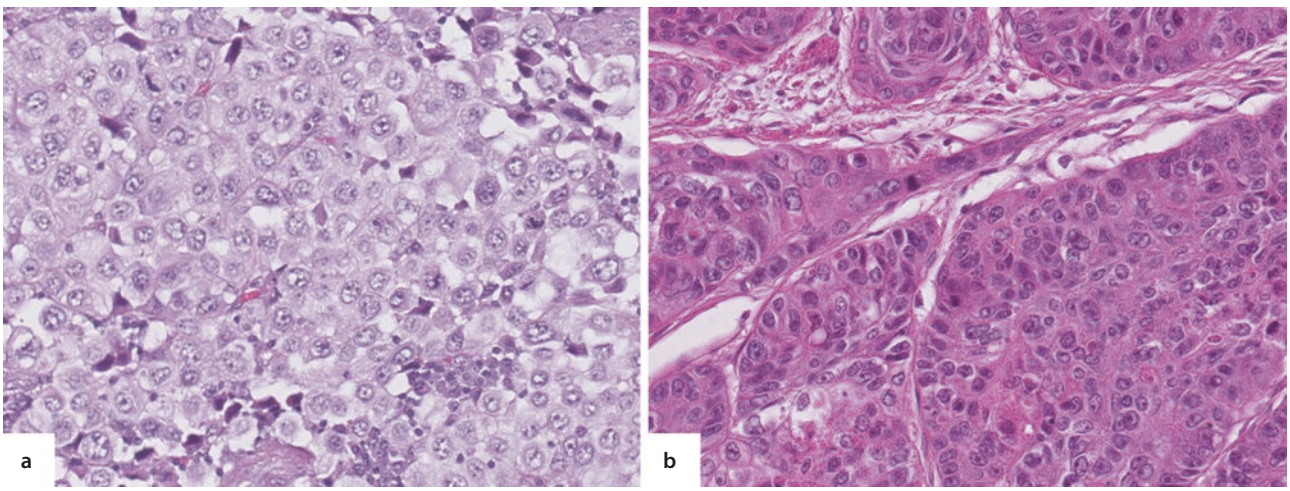

Fig. 3.8 Alteration of nuclear chromasy in malignant tumor: chromatin may be coarse, clumped, and distributed along the nuclear membrane, giving a pale appearance to the nucleus **a** or darkly stained, giving hyperchromasia to the nucleus **b**

3.4 Dysplasia

The term *dysplasia* refers to an anomaly of growth and differentiation, typically in epithelia. Dysplasia is characterized by some pathological microscopic features, namely, increase in thickness, architectural disorder, pleomorphism, nuclear enlargement with hyperchromasia, and presence of increased number of mitoses; mitoses are also present in abnormal locations and may be observed in superficial layer rather than exclusively in the basal epithelial zone [11]. These architectural and cytological atypia do not exceed basement membrane but represent a predisposition for progression to invasive neoplasia: dysplasia is a preneoplastic lesion. However, the progression to cancer is not changeless, and mild and moderate dysplasia may be reversible by removing the triggering cause [12].

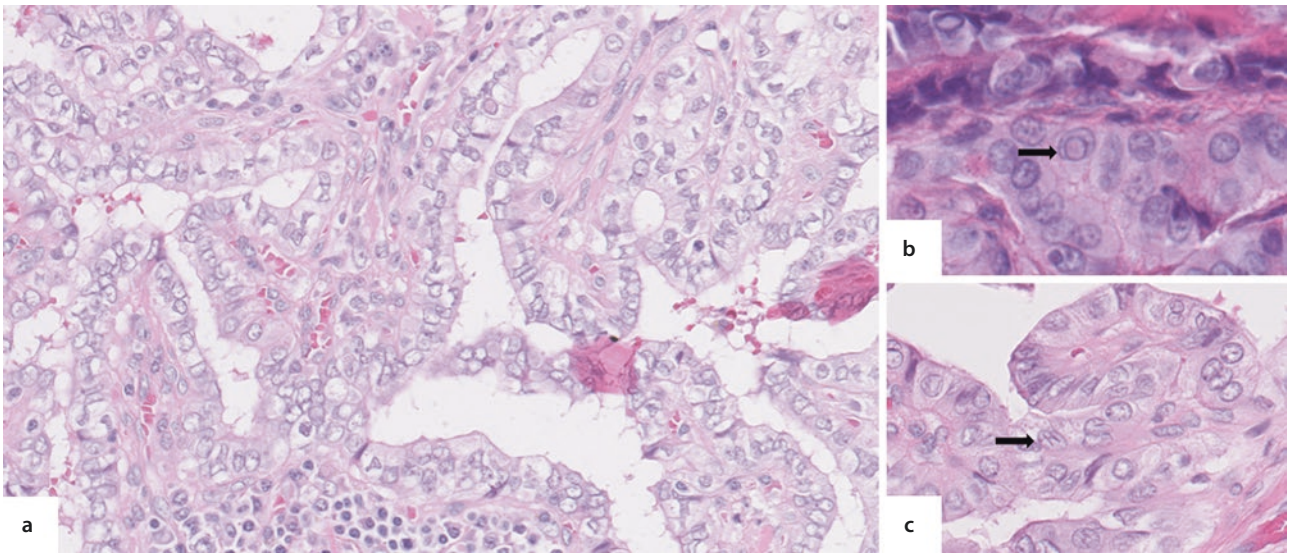

Fig. 3.9 Nuclear hallmarks of papillary thyroid carcinoma: note pale nuclei with powdery chromatin ("Orphan Annie" nuclei) **a**, intranuclear cytoplasmic inclusion (**b**, arrow), and longitudinal nuclear grooves (**c**, arrow)

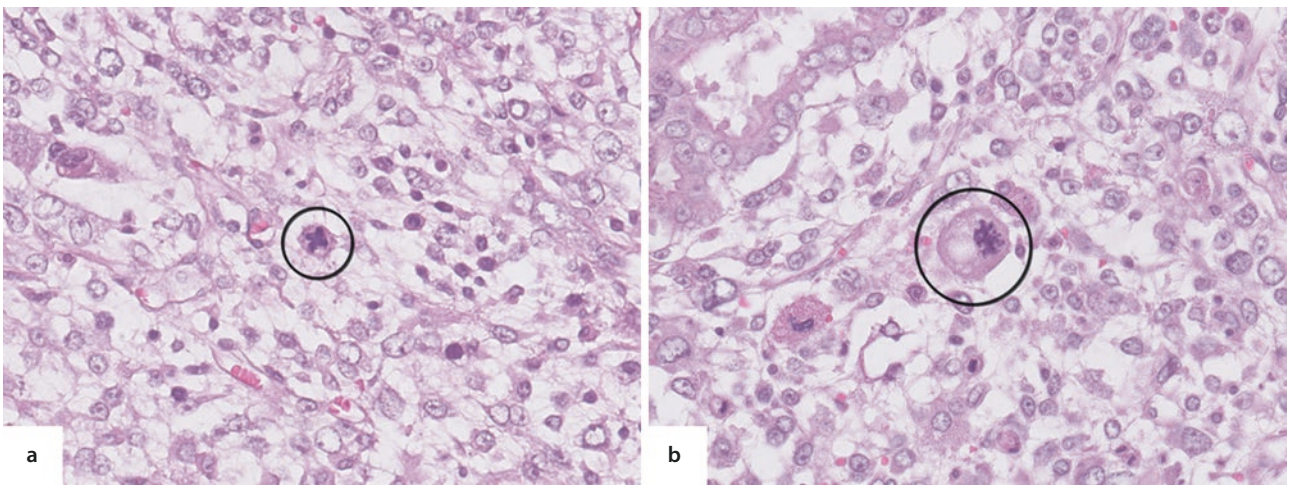

Fig. 3.10 In poorly differentiated malignant neoplasms, an increase in the number of mitoses can be observed, even with an atypical appearance, such as quadripolar (A) or bizarre (B) mitotic figures

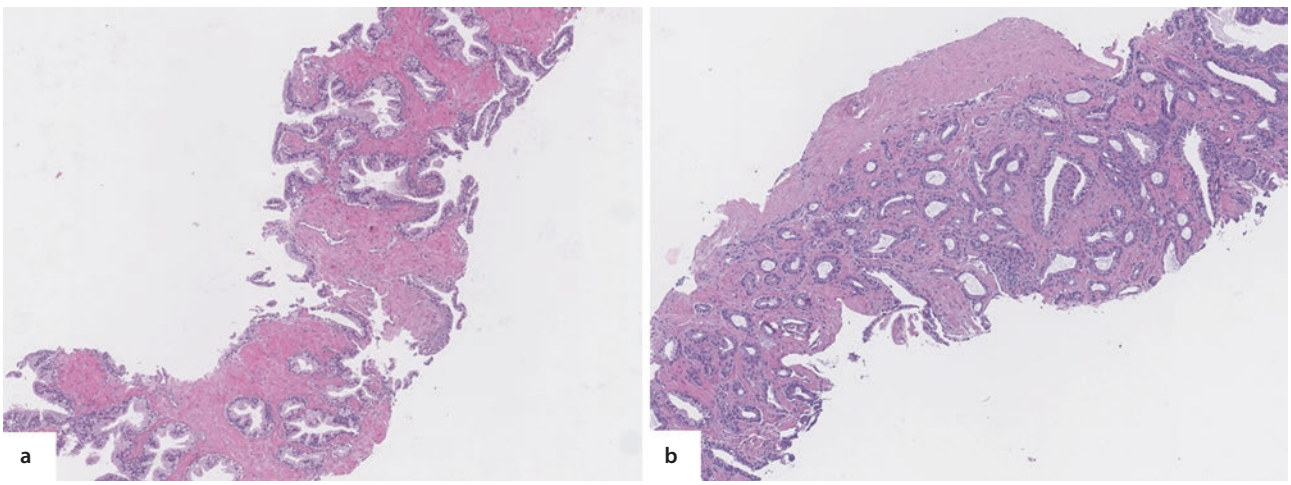

Fig. 3.11 The Gleason grading system is based on the assessment of glandular differentiation: compared to the normal prostatic tissue **a**, neoplastic glands are typically smaller and more packed **b**

Dysplasia is generally graded as "mild," "moderate," and "severe," depending on the extent and severity of morphological changes, and these criteria are generally applicable to the epithelia of all districts:

Mild dysplasia: This is characterized by proliferation of basal and parabasal cells limited to the lower third of the epithelium. Cytological and architectural atypia are minimal and mitoses are not prominent.

Moderate dysplasia: This involves the lower half of the epithelium with loss of basal polarity; stratification and maturation are preserved. The cytological changes are more prominent and increased; atypical mitoses may be present in the basal layers.

Severe dysplasia: Architectural and cytological changes can be very prominent, extending from the basal layer into the upper third of the epithelium. Suprabasal layer mitoses are usually present, even featuring atypical mitotic figures.

Carcinoma in situ is defined as severe dysplasia involving the entire thickness of the epithelium but being still confined to the normal tissue. The invasion of basement membrane defines the lesion as invasive carcinoma.

3.5 Grading

Pathological grading is a qualitative assessment that refers to the degree of differentiation of tumor cells and expresses it through a score. The most common grading system uses a four-grade score, depending on the degree of anaplasia: grade 1 tumors are well-differentiated and, although atypical, neoplastic cells resemble parent tissue. Conversely, grade 4 tumors are so anaplastic that even the recognition of their cell of origin becomes difficult; grade 2 and 3 tumors have intermediate features [13].

For many cancer types, site-specific grading systems are used, based on different pathological features.

Prostate cancer: The most widely used grading scheme worldwide is the Gleason system [14, 15]. The Gleason grading system is based on the histologic pattern of arrangement of carcinoma cells in H&E-stained prostatic tissue sections. The method assesses the glandular differentiation (neoplastic glands are typically smaller and more packed than benign glans) (Fig. 3.12) and the histologic pattern of growth of the tumor in the prostatic stroma, assigning a grade pattern from 1 to 5:

Gleason pattern 1: very well-differentiated growth of closely packed but separate, uniform, rounded to oval, medium-sized acini.

Gleason pattern 2: increase in variability in gland size and shape. The glands are not as circumscribed as pattern 1.

Gleason pattern 3: well-formed, individual glands of various sizes, including branching glands.

Gleason pattern 4: includes poorly formed, fused, and cribriform glands.

Gleason pattern 5: individual cells and cords or sheets of cells; solid nests of cells with occasional gland space formation are observed. Necrosis may be present.

The primary grade pattern (the most common seen in the tumor) and the secondary grade pattern are used to generate a histologic score, which can range from 2 to 10; each score falls into prognostically relevant Grade Groups.

Breast cancer: The most common grading system for breast cancer is the Nottingham Histologic Score system (Elston-Ellis modification of Scarff-Bloom-Richardson grading system) [16]. This method evaluates three morphological features (Fig. 3.13):

- Amount of gland formation
- Nuclear features (variation in size and shape, chromatin appearance)
- Mitotic activity

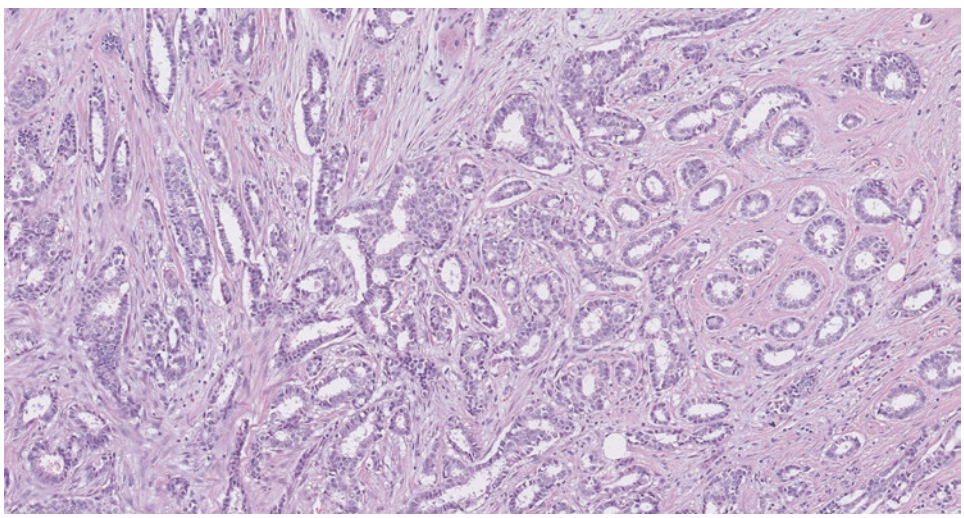

Fig. 3.12 Breast ductal carcinoma grade 1 s. Nottingham Histologic Score system: evident glandular formation, bland nuclear atypia, and low mitotic rate

Each of these features is scored from 1 to 3, and then each score is added to give a final total score ranging from 3 to 9. The final total score is used to determine the grade:

- Grade 1: score of 3–5
- Grade 2: score of 6–7
- Grade 3: score of 8–9

Malignant neoplasms are often characterized by morphological and phenotypic tumor heterogeneity, and then areas with different grade of differentiation may be present; if there is evidence of heterogeneity, the highest grade must be considered and reported.

The prognostic impact of grading is noticeable for some tumors [14, 17, 18] (i.e., sarcoma, breast and prostate carcinoma), but generally there is no direct correlation between pathological grading and clinical behavior.

3.6 Staging

Stage refers to the extent of cancer in the body and is a fundamental prognostic factor, which affects the therapeutic approach. Among the various existing cancer staging systems, the most clinically exploited is the tumor (T), node (N), and metastasis (M) staging system, developed by AJCC (American Joint Committee on Cancer) and UICC (Union for International Cancer Control) [19]. The AJCC TNM staging system provides both clinical and pathological assessment of tumor extension: the clinical stage (cTNM) is based on physical examination and imaging study information (ultrasound, computed tomography, magnetic resonance, positron emission tomography, etc.) and is integrated and/or modified by pathological evaluation of the resected specimens (pTNM). In the pTNM assessment:

- The *T* refers to the size and extent of the main tumor, measured to the nearest whole millimeter; size may be adjusted based on microscopic examination. pTis is assigned to in situ *neoplasia* identified by microscopically examination of a surgical resection .
- The *N* refers to the number of nearby involved lymph nodes. Microscopic assessment of a node may be performed by fine needle cytology (FNC), core biopsy, excisional biopsy, and regional lymph node dissection. Many cancer types have specific recommendation regarding the minimum number of lymph node to be evaluated to provide prognostic information (i.e., colon cancer).
- The *M* refers to the presence of distant metastases, spatially separated from the tumor. Direct extension of a primary tumor into a contiguous organ is classified as part of the tumor and not as metastasis.

An example of specific staging system for a single neoplasm is represented by the Ann Arbor staging system [20] for Hodgkin lymphoma (HL): the stage is mainly determined by location of the tumor (single or multiple regions, both sides of the diaphragm, extralymphatic organ involvement) and presence of constitutional symptoms. Other pathological features considered are the extension from the lymph node to adjacent tissue and presence of lesions >10 cm in diameter ("bulky" lesion).

3.7 Conclusion

The terms benign and malignant tumor refer to the clinical and biological behavior of a neoplasm as well as some specific morphological features including differentiation, modality, and rate of growth and metastatic capability. Fundamental prognostic factors are the qualitative assessment of the degree of differentiation of malignant tumor cells (grading) and the extent of cancer in the body (staging). Histopathological features of tumor should be integrated with physical examination and imaging study information for an accurate diagnosis and a proper patient management.

Summary of Clinical Recommendations

- Histopathological features of tumor should be integrated with clinical and imaging data for an accurate diagnosis and a proper patient management.
- The pathologist's decision-making process should be guided by evidence-based guidelines and consensus recommendations.
- The College of American Pathologists (CAP) provides guidelines for collecting the essential data elements for complete reporting of malignant tumors (Cancer Protocol Templates).

Key points

- Benign and malignant tumor can be differentiated according to differentiation, modality of growth, rate of growth, and metastatic capability.
- Malignant neoplasms have the capability to invade and destroy surrounding tissue and metastasize to distant sites.
- Histopathological features of tumor should be integrated with clinical and imaging data for an accurate diagnosis and a proper patient management.

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