Recent Advances in Histopathology

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Contents

Chapter 10

Breast metastases from extramammary malignancies

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NTRODUCTION

It is common knowledge that the incidence of primary malignant tumours varies from one organ to another. Likewise, the ratio of primary malignant tumours and metastases varies from one organ to another. In some organs, such as liver or bones, metastases are more common than primary malignancies, whereas in others, like prostate or skin, primary carcinomas are much more common than metastases from other sites.

Metastases to the breasts are considerably less common than primary breast carcinoma. However, the literature about these secondary tumours is quite copious, indicating that these metastases to the breasts may present considerable diagnostic problems. Furthermore, they may be inadvertently misdiagnosed if examined without additional clinical data, good imaging workup and well-planned targeted immunohistochemical studies.

CLINICOPATHOLOGIC DATA

How common are metastases to breasts?

Metastases of solid malignant tumours to breasts are uncommon, accounting for approximately 0.5–2% of all breast tumours in surgical pathology material [1–4]. Comparable data have been reported from fine-needle aspiration biopsy studies [5]. In autopsy material, which usually includes terminal cancer patients with widespread dissemination of cancer, the involvement of breasts by metastatic cancer may be even higher [4,6].

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What are the most common malignant neoplasms that have metastasised to the breasts?

During the last 30 years there were several articles in which the authors presented cases seen or collected in their medical centres; and many of them reviewed previously published articles [1–11]. Some of the major findings have been consistently confirmed; some details varied slightly and there were some controversies and disagreements.

Toombs and Kalisher [7] reported 21 cases from their practice or retrieved archives and analysed additional 131 cases reported in the literature prior to their publication. The general conclusion is that the most common tumours which have metastasised to the breast are melanomas and haematologic malignancies classified as leukaemia or lymphoma, followed by lung carcinomas, and thereafter carcinomas of the gastrointestinal tract and female genital organs. In this study, as well in all others that will be mentioned here, women outnumbered men by a large margin.

Alva and Shetty-Alva [8] reviewed the MEDLINE data and 24 articles presenting data from 1855 to 1998 but excluding haematopoietic neoplasms. In their search, they found 431 reported cases of tumours metastatic to the breast. The primary sites for metastasis to the breast they found are listed in **Table 10.1**.

The papers from major US cancer centres contain more or less similar data. Scientists from the University of Texas MD Anderson Cancer Center analysed their data from 1983 to 1998 and identified 169 patients who had metastasis to the breast from non-breast solid organ primary tumours [9]. The most common tumours were melanomas (38.5%). Most patients (149 or 88.2%) had a prior history of cancer, and 91 (53.9%) patients presented with additional systemic metastases. The median survival from the time the breast metastasis was diagnosed was 10 months (range, 0.4–192.7). Premenopausal women were more often affected than postmenopausal women.

The study from the Memorial Sloan Kettering Cancer Center, based on material from 1990 to 2010, is probably the most informative about breast metastasis patients in present times [3]. It shows that melanoma is the most common malignant tumour metastasising to the breasts. It is followed by carcinoma of the ovary, lung and gastrointestinal tract. If these tumours are grouped histogenetically, the largest group were carcinomas (51%, most often originating from female genital organs, lungs and gastrointestinal tract), followed

Table 10.1 Primary tumours metastasised to the breast [8]

Organ	Number of cases	%
Skin (malignant melanoma)	87	20.2
Lung	78	18.1
Ovarian	50	11.6
Prostate	39	9.0
Kidney	24	5.6
Stomach	15	3.5
Ileum	13	3.0
Thyroid carcinoma	12	2.8
Uterine cervix	12	2.8
Other	101	23.4

by melanoma (21%) and sarcomas (21%). The overall mean age of patients at the time of diagnosis was 51 years, and 85% were females. Unilateral tumours predominated and only 12% were bilateral. Most presented in form of a solitary nodule (75%). In most patients, there was evidence of widespread malignant disease and metastases to other organs were present in 77% of all cases. Survival varied from one patient to another but in most of them the prognosis was abysmal, and the mean survival was only 15 months after the diagnosis of breast metastasis.

The data stemming from other continents differ from those from North America. A report from China indicates that the most common tumours metastasising to the breast were lung carcinoma and nasopharyngeal carcinoma, reflecting the high prevalence of these two forms of cancer in that country [10]. Yet another paper from China stated that the most common cancer metastatic to the breast were malignancies of lung and stomach [11]. In all these studies, women significantly outnumbered men, and most were under the age of 50 years.

The statistics about metastatic tumours to the breast change somewhat if the authors were to include not only solid tumours but also haematologic neoplasms. A study from Italy comprising both solid tumours and haematologic neoplasms reported that lymphomas were the most common secondary malignancy of the breast [12]. The data from South Korea, which also include haematologic neoplasia, indicate that under these conditions lymphoma is the most common diagnosis for metastatic tumours in the breast [13].

Medical literature is replete with case reports of rare and/or unusual tumours that have metastasised to the breast. For example, Yu and Zhou [14] reported an ileal neuroendocrine tumour that had metastasised to the breast and reviewed a few previously reported similar cases. Zagami et al [15] reported four other neuroendocrine tumours metastatic to the breast, two of which to both breasts.

Ibisevic et al [16] reported a rare case of uterine leiomyosarcoma that had metastasised to the breast. These authors also presented in a tabular form 11 previously published malignant uterine smooth muscle tumours that had metastasised to the breasts.

Pappi et al [17] described a primary Ewing sarcoma of the breast. Stimulated by that unusual diagnosis they perused the literature and discovered reports of several other primaries and metastatic Ewing sarcomas in the breast.

Do et al [18] reported an amelanotic melanoma of the breast and reviewed four other case reports of amelanotic melanoma of the breast. Amelanotic melanoma is a rare form of melanoma, accounting for 2–8% of all melanomas. In the breast case reported by Do et al, no extramammary primary melanoma could be found and thus it was most likely a primary breast tumour. They also found reports of four other amelanotic melanomas of the breast. Three of these had no evidence of a possible primary extramammary melanoma and were thus most likely primary melanomas of the breast. Only the fourth case had an identifiable primary and was thus *bona fide* a metastasis to the breast. As detailed in an intriguing case report of a breast melanoma by John et al [19], the authors elaborate how any melanoma of breast, primary or metastatic, may be a diagnostic challenge for pathologists and requiring extensive immunohistochemical work-up.

How common are metastases from the primary breast carcinoma to the contralateral breast?

Approximately 2–12% breast cancer patients will develop synchronous or metachronous cancers in the contralateral breast [20]. The incidence of synchronous cancers, defined as

those that are diagnosed within 1 year of the diagnosis of the first cancer on the other side, seems to increase in the US [21]. In this study, performed on the 'Surveillance, Epidemiology, and End Results (SEER)' database (1973–2014), Sakai et al identified 11,177 women diagnosed with contralateral breast cancer. In this cohort 4,228 (38%) had synchronous breast cancers and 6,949 (62%) had metachronous cancers, diagnosed 1 year or later after the initial diagnosis. The incidence of synchronous cancers increased significantly from 1.4% in 1975 to 2.9% in 2014, but the reasons for this increase are not known.

In contrast to these epidemiologic data, which are consistent with a de novo formation of cancer in the contralateral breast, previous authors claimed for many years that the most common form of bilateral breast cancer is metastasis from a cancer in one breast to the other [22,23]. Other authors [2,3,8] quoted these articles as evidence that in most cases of bilateral breast cancer, a cancer in one breast had metastasised to the other.

However, autopsy study data collected by Cifuentes and Pickren [24] do not support this point of view. These authors showed that breast cancer metastases to the contralateral breast do occur, but even in autopsies performed on deceased terminally ill patients they were not common: in 707 autopsied breast carcinoma patients, multiple metastases were found in 137 cases, but metastases in the contralateral breast only in 31 of these cases, which represents 4% of all autopsied breast cancer patients [24].

Modern molecular biology techniques have definitively shown that in most cases of bilateral breast cancer, the two tumours have developed independently [25,26]. These novel data show that only a small number (about 6%) of bilateral breast cancers the two tumours are clonally related, confirming that one of them is a metastasis from the other. The conclusion is that, in the vast majority of cases of bilateral breast carcinoma, two separate primaries have developed both with their own characteristic molecular pathogenesis.

How do solid tumours metastasise to the breast?

Metastases may reach the breasts through haematogenous or lymphatic routes [13,27]. Metastases from distant organs are mostly haematogenous, whereas lymphatic metastases are more common from head and neck cancers, and some carcinomas from thoracic organs. The rare metastases from one breast to another also occur through lymphatics. It has been suggested that some gastric and even some ovarian carcinomas may reach the breast through lymphatics [28–30].

Haematogenous metastases are most often located in the outer upper quadrant of the breast, which is also the location of most primary breast carcinomas [31]. Many metastases are found inside the well vascularised breast parenchyma, others have been found in subcutaneous tissue, and some may resemble inflammatory breast carcinoma. Most often, they form a distinct mass, separate from the glandular portion of the breast [31].

A single palpable painless mass located in the upper outer quadrant of the breast is the most common initial clinical feature reported in several studies [6,13,30,31]. However, multiple nodules have been found in about 20–30% of cases. Some cases present clinically with bilateral metastases and occasionally such bilateral tumours are even the first sign of malignancy [32].

Lymphogenous breast metastases are less common than haematogenous metastases. Their features include diffuse skin thickening and obliteration of the subcutaneous fat, and possible lymphedema due to obstruction of draining lymphatics by intravascular tumour growth. Typically, these metastases are hypoechoic, and may be associated with enlargement of axillary or internal mammary lymph nodes [13]. Metastatic tumours to the

breast are less often accompanied by metastases to the axillary or intramammary lymph nodes than primary breast carcinomas.

None of these clinicopathologic findings is pathognomonic of a specific metastatic route; haematogenous metastases cannot be distinguished with certainty from those that occurred through lymphatics [27]. Accordingly, the route of metastasis is not discussed in most clinical studies. The most important task of clinicians and pathologists alike is to properly diagnose a breast tumour as potentially metastatic, and thus distinguish it from primary breast carcinoma [31–37].

Is there a standardised approach to diagnosing tumours that have metastasised to the breasts?

Since metastases to the breast are quite rare, they are usually not included in standard pathological differential diagnosis of breast neoplasms. By default, the workup of such cases often results on the list of 'unexpected diagnoses'.

To illustrate the complexities of histopathologic diagnosis we are including several cases from the files of the Department of Pathology of the University of Michigan which were not so easy to diagnose as they metastasised to the breast.

Figure 10.1 shows an ovarian low-grade serous carcinoma metastatic to the breast. The patient was known to have had an ovarian carcinoma, but the metastasis appeared higher grade than the original tumour from which it arose.

Figure 10.2 shows a metastasis of an endocervical carcinoma which mimicked an invasive ductal carcinoma of the breast.

Figure 10.3 shows a metastasis of a high-grade endometrial adenocarcinoma showing no microscopic evidence of its endometrial origin.

Figure 10.4 shows a metastasis of an atypical carcinoid that still has some resemblance to the carcinoid from which it arose but shows more nuclear atypia.

Figure 10.5 shows the metastasis of a neuroendocrine carcinoma of the lung presenting as a high-grade tumour which would have been hard to classify without immunohistochemistry; it revealed that the tumour was neuroendocrine.

Figure 10.6 shows a diffuse large B cell lymphoma replacing normal breast parenchyma.

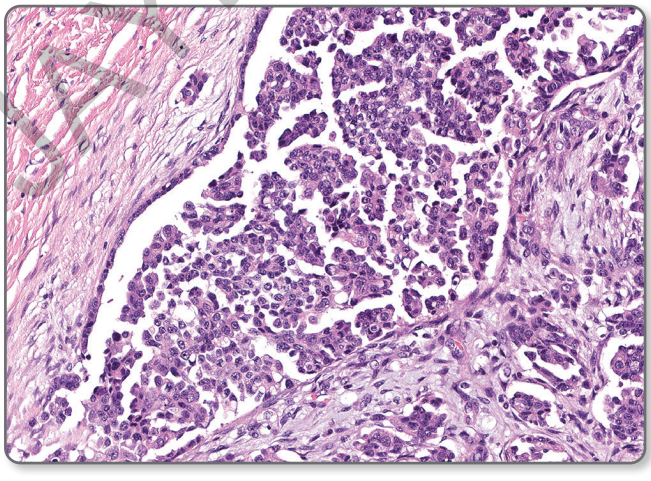


Figure 10.1 Low-grade serous carcinoma ovary metastatic to the breast.

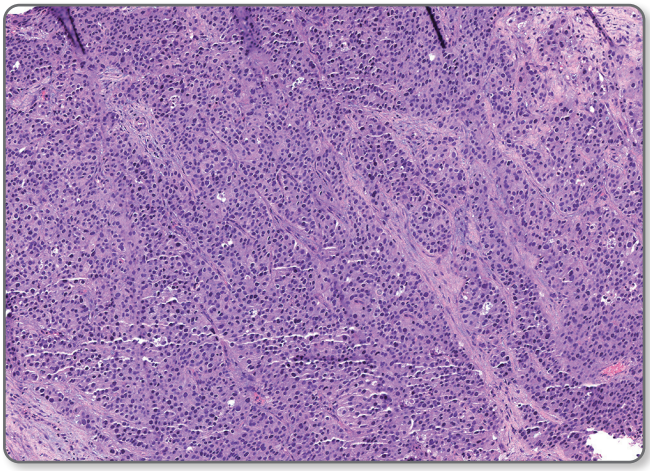
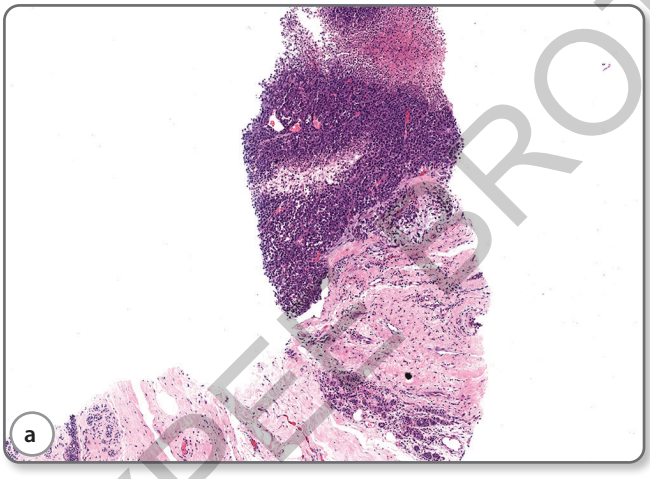


Figure 10.2 Breast metastasis of an endocervical carcinoma mimicking invasive ductal carcinoma of the breast.



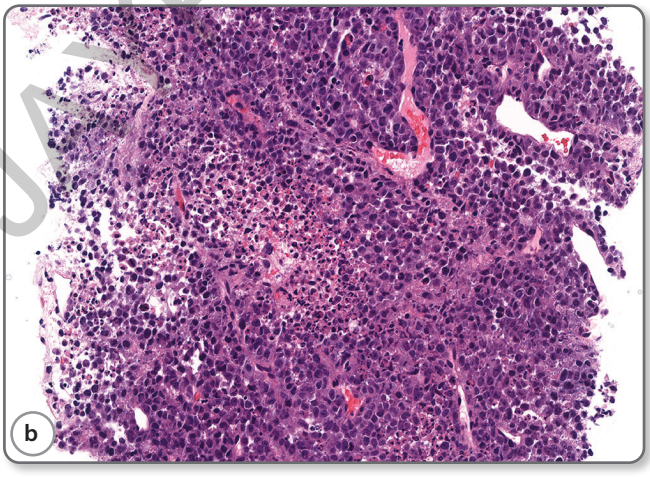


Figure 10.3 Breast metastasis of a high-grade endometrial adenocarcinoma.

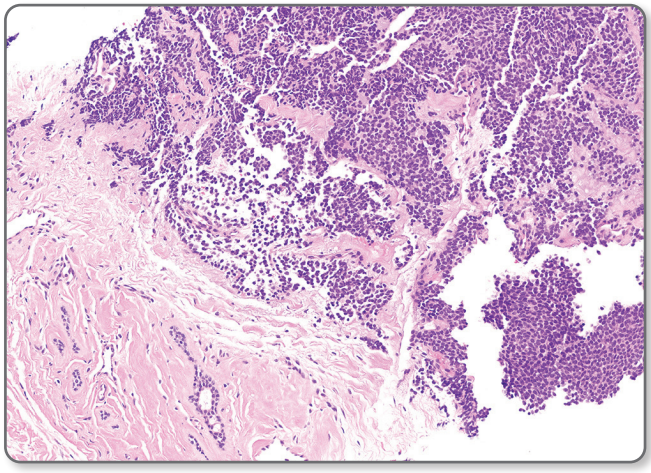


Figure 10.4 Breast metastasis of a pulmonary atypical carcinoid.

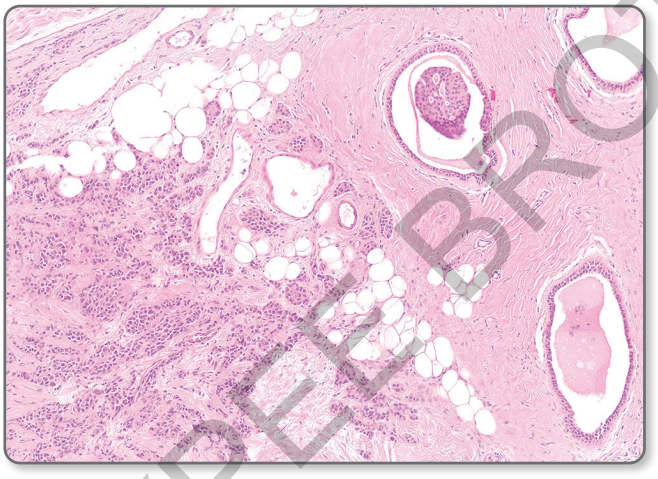


Figure 10.5 Breast metastasis of a neuroendocrine carcinoma of the lung.

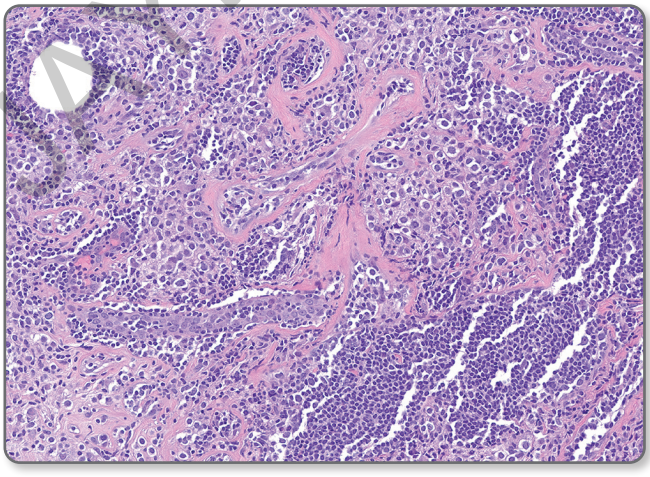


Figure 10.6 Diffuse large B-cell lymphoma invading the breast and replacing the normal parenchyma.

To avoid any unwarranted surprise, it is wise to use a systematic tripartite approach including a detailed clinical history, imaging studies and microscopic examination of the tumour and use of well-chosen immunohistochemical markers.

The first step to a correct pathologic diagnosis is to recognise that the metastatic tumour inside the breast does not have the classical pathological features of a primary breast carcinoma, in other words 'does not belong there'. Once the pathologist realises this, it is wise to revisit detailed relevant patient data and inquire about patient's medical records to determine if there is any mention of prior malignancy. Published reports indicate that >70% of all such patients have a history of cancer [8,13,37].

If there is no history of another cancer, or a previously treated cancer, it is worth remembering that a metastasis to the breast may be the first and only sign of a hidden primary, and thus alert the surgeon or the oncologist to search for a possible primary tumour [31–33]. Metastases to the breast are more common in younger, premenopausal women; any fast-growing mass in the breast of a younger woman or even adolescent should be considered as a possible metastasis [9,13]. Women are more likely affected than men, but it is worth remembering that in several studies about 15% of cases were men [2–4,9,10].

The next step is to examine the imaging reports to see if the mammography or sonography or other scanning modality studies have noticed anything unusual in the breast [13,34,35]. As mentioned before, rapidly growing solitary masses that by ultrasound appear to be hypoechoic, and on imaging lack malignant microcalcifications, spiculation or architectural distortion, and lack of a significant desmoplastic reaction around the tumour are atypical for primary breast carcinoma. Accordingly, these findings are more often signs of a metastasis than of a primary breast tumour. However, breast metastases may show variable ultrasound features and in some cases the distinction between a metastasis and a primary breast cancer or a benign breast lesion may be quite difficult.

Certain microscopic findings may suggest that a lesion is not a primary breast neoplasm. For example, lack of intraductal preinvasive carcinoma in adjacent breast tissue, lack of calcifications or oestrogen receptor (OR) negativity in a well-differentiated adenocarcinoma could be all warning signs [36,37]. Melanin pigment in a high-grade epithelioid neoplasm is suggestive of melanoma, and psammomatous calcification in a micropapillary adenocarcinoma is suggestive of papillary serous ovarian carcinoma [28,31]. Hepatoid features are indicative of a metastasis from a primary liver cancer [38]. Squamous cell carcinoma in a breast biopsy is more likely a metastasis than a primary [36].

Final correct pathological diagnosis is usually made by a targeted immunohistochemical panel, which are assembled depending on the microscopic features of the tumour at hand [39]. The most widely used approach begins with immunohistochemistry for some well-known markers considered to be useful for the identification of normal and/or neoplastic breast parenchymal cells. This panel of immunostains includes antibodies to the following markers: OR, GATA3 (GATA transcription factor binding protein 3), cytokeratin-7 (CK7), pancytokeratin and Sox-10 (SRY-related HMG-box family transcription factor 10). A panel of stains must be used because none of these markers is specific for breast tumours and many markers listed here are also expressed in other neoplasms. However, if the tumour cells immunoreact with all or most of these antibodies, using the usual caveats about specificity of certain antibodies, the tumour is most likely a primary breast carcinoma.

If the tumour under study is a non-breast adenocarcinoma, the second step of the work-up will be to try to determine its primary organ of origin. For lung adenocarcinomas recommended markers are thyroid transcription factor 1 (TTF1) and napsin A; for gastrointestinal cancers CDX2, CK7 and CK20; and for ovarian high-grade serous carcinoma OR, *WT-1* (Wilms' tumour-1) and *PAX8* (paired box gene 8). For melanoma, it is best to use target *Melan A*, Sox-10 and HMB-45 (human melanoma black-45). For neuroendocrine tumours, the panel will include chromogranin and synaptophysin. For various spindle cell neoplasms, various sarcoma markers will be used, and lymphoid markers for high-grade lymphomas.

THE MOST IMPORTANT FACTS LEARNED FROM CLINICOPATHOLOGIC CORRELATION STUDIES

- Metastases to the breasts occur rarely and account for only 1.5–2% of all malignant tumours in that anatomical site
- The most common malignancies metastasising to the breasts are melanoma, lymphomas and carcinomas of the lungs and gastrointestinal tract
- Metastases of breast carcinoma to the contralateral breast are uncommon, and most bilateral breast carcinomas represent separate tumours originating separately one from another
- Metastatic tumours in the breast may be synchronous or metachronous with the primary from which they have originated. They are more often found in women than in men
- Metastatic tumours are found more often in the breast of premenopausal than postmenopausal women
- Breast metastases are usually found in women known to have cancer, and other metastases are found in most of them; but in many cases such metastases are the first or the only sign of a malignant disease

Key points for clinical practice

- The most productive approach to correct pathologic diagnosis of metastatic tumours in the breast is based on three-pronged approach which includes detailed clinical history, good imaging support and histopathologic examination of the tumour with targeted immunohistochemistry.
- Any rapidly growing tumour of the breast in a premenopausal woman deserves to be considered as a potential metastasis from some other site, until proven otherwise.
- The first inkling that a tumour might be a metastasis is when the pathologist on microscopic examination realises that, histopathologically, the tumour does not have the features of breast cancer, colloquially said 'does not belong there'.
- The definitive histopathological diagnosis is made by targeted immunohistochemistry.
- Immunohistochemistry is used to show that the tumour does not express the usual breast cancer markers.
- Detection of immunohistochemical markers specific for other malignant tumours except breast cancer is important for finding the primary from which the breast metastasis originated.

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Recent Advances in Histopathology

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This volume presents a collection of in-depth reviews dealing with recent developments in histopathology. The chapters are written by recognised experts in an accessible and easy-to-read format supplemented with judiciously chosen colour microphotographs. For quick review and additional emphasis, each article is further enhanced by a set of bulleted 'key points for clinical practice', summarising the message and pin-pointing the clinical relevance of the presented material for the daily practice of histopathology.

This volume opens with a chapter on basic principles of machine learning and how artificial intelligence is contributing new approaches to solve old problems in diagnostic histopathology. Further topics addressed include (among others):

- Choriocarcinoma
- Poorly differentiated carcinomas of the thyroid
- Classification of thymomas
- Classification of odontogenic tumours
- Tumours of the biliary tract
- Plasma cell neoplasms

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