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HISTORY OF ANATOMIC PATHOLOGY
Antonio Ascenzi (1915-2000), a Pathologist devoted to Anthropology and Paleopathology
V. Giuffra, S. Minozzi, S. Marinozzi, G. Fornaciari

Antonio Ascenzi is well known within the scientific community for his original contributions to morbid anatomy and in particular for his studies on the fields of bone biology, bone biomechanics, haematology and congenital heart disease. Additionally, Ascenzi was also interested in human evolution and applied his deep knowledge of pathology to ancient human remains, conducting research in paleo-anthropology on fossilized Neanderthal specimens found in Italy. The name of Ascenzi is linked with the discovery and study of the most ancient Italian bone fossils, namely the Ceprano skull, an early specimen of Homo erectus. Furthermore, his pioneering researches on the Uan Muhuggiag and Grottarossa mummies and his rigorous studies on several aspects and problems concerning the pathologies of past human populations made him a pioneer in the fields of Italian mummification and paleopathology. The thread that linked his diversified research interests outside and within human anthropology was a profound passion for the search and discovery of scientific truth.

ORIGINAL ARTICLE
Expression of p16 in abnormal pap-tests as an indicator of CIN2+: a possible role in the low grade ASCUS and L/Sil (lg) cytologic lesions for screening prevention of uterine cervical tumours

The aim of this study was to assess the validity of protein p16 expression as an indicator of progression in lesions as ASC-US and L-SIL. For this purpose, we examined 246 cytological samples (91 ASC-US, 60 L-SIL, 36 ASC-H, 59 H-SIL) of which 151 were conventional Pap-tests (CC) and 95 in liquid based cytology (LBC) with colposcopic and histology follow-up. The results showed that in the positive P16-Pap-tests a 59% PPV vs CIN2+ in all cytologic diagnoses compared to 43% in cytologic reading alone. 96% of HG cytologic lesions were positive for p16, and the data showed good correlation between positivity for p16 in the cytologic preparations and the presence of CIN2+ lesions in the histologic test (chi-square for trend = 0.0001). The sensitivity, specificity and NPV were 93%, 52% and 91%, respectively, in all cytologic diagnostic categories. P16 was positive in 46% of ASC-US and 53% of L-SIL. The PPV vs expressed CIN2+ was higher than that observed in cytologic reading (48% vs 26%, and 31% vs 20%, respectively). The specificity was 83%, the specificity 67% and 54%, respectively, and the VNP was 92% and 93%. It is possible to design algorithms for colposcopic follow-up that can reduce the need to obtain a follow-up. The future application of this test may allow the creation of a bio-molecular automated pap test.

REVIEW
Pathologic examination and staging of rectal carcinoma: a critical review
P. Greco, G. Magro

In rectal carcinoma, accurate pathological examination is crucial for a correct staging and identification of predictors of risk of both local recurrence and overall survival. Accordingly, surgical pathologists determine many facets of rectal carcinoma patient care. Although rectal carcinoma shares many pathologic features with colon carcinoma, however, the anatomical location of the rectum poses additional problems in formulation of a pathological report. The most critical issues of pathological examination in rectal carcinoma involve assessment of: i) surgical resection margins (distal and circumferential resection margins); ii) total mesorectal excision (the plane of surgery); iii) peritoneal serosa involvement; iv) distance of invasion beyond the muscularis propria; v) number of lymph nodes to be recovered; vi) mesorectal tumour deposits; and vii) histologic regression grade after preoperative chemoradiotherapy. Although seemingly straightforward, the definition and macroscopic/microscopic interpretation of these key pathological features are still controversial, and lead to pathological reports that are variable not only among the different institutions but even within a single institution. The aim of this critical review on rectal carcinoma is to discuss confusing and/or challenging pathological problems, especially those with clinical impact, in order to provide a checklist that is useful for practicing surgical pathologists.

CASE REPORTS
Lipoma with osteocartilaginous metaplasia: case report and literature review
G.M. Vecchio, R. Calabiano, A. Garrera, S. Larzafame

Osteocartilaginous metaplasia in lipomas is rare and mainly encountered in large-sized, long-standing lipomas. This entity can be found at almost any site of the body, particularly in the soft tissues of the skeletal system, breast, pharynx, and nasopharynx. We describe a case of lipoma with osteochondroid metaplasia in a 65-year-old woman with an indolent lesion, and discuss differential diagnoses.

Hemangiopericytoma-solitary fibrous tumour of soft tissue: description of a case showing atypical histological features
M. Zanelli, L. Andreini, G. Galanti, S. Corteccia, R. Nannini, A. Bondi

Extrathoracic solitary fibrous tumours have been reported in almost all anatomic sites, but reports of tumours in the extremities or in intramuscular locations, as well as of tumours with atypical histological features and malignant behaviour, are rare. Herein the authors describe a case of hemangiopericytoma-solitary fibrous tumour that arose in the gluteal region of a 47-year-old woman. The tumour showed atypical histological features, such as high cellularity, increased mitotic activity and focal expression of cytokeratins.

The use of placental S100 (S100P), GATA3, and Napsin A in the differential diagnosis of primary adenocarcinoma of the bladder and bladder metastasis from adenocarcinoma of the lung
M.R. Raspolini, C.E. Comin, A. Crisci, M. Chilosi

Primary bladder adenocarcinoma accounts for 0.5-2% of all malignant bladder tumours. Literature data indicate the bladder as the second most common site of metastatic genitourinary tumours, with the kidney as the most frequent location. Secondary tumours of the bladder account for about 2.3% of all bladder malignancies encountered in surgical specimens. Herein, we describe an adenocarcinoma deeply infiltrating the bladder wall, with no morphologic features of transitional cell carcinoma, in a patient with a previous diagnosis of primary lung adenocarcinoma, mixed subtype. In this case, the use of a limited immunohistochemical panel including napsin A, a recently described highly sensitive marker for lung adenocarcinoma, GATA3 and S100P, two novel markers of urothelial differentiation, was of crucial importance in differentiating between lung adenocarcinoma metastatic to the bladder and primary bladder adenocarcinoma.

Cystic struma ovarii: a report of three cases
C. Manini, A. Magistris, M. Puopolo, P.L. Montironi

Three cases of cystic struma ovarii in women aged 16, 20 and 40 are described. All patients had an asymptomatic ovarian mass at ultrasound scan. The tumours, all of which were unilateral and confined to the ovary, ranged from 7 to 10 cm in the greatest dimension. Two lesions were unilateral, the third multilocular, and all were filled with green fluid. Microscopic examination showed follicles with fibrous walls and non-specific inflammatory epithelial cells. In the wall of the cysts, there was a small number of thyroid follicles. In one case, an association with a cystic mature teratoma was seen. The paucity of thyroid follicles and the non-specific appearance of the epithelial cells required a careful sampling and immunohistochemical staining for thyroglobulin to establish an exact diagnosis. The postoperative period was uneventful and thyroid function remained normal. In conclusion, cystic struma is probably often underdiagnosed and should be considered when evaluating cystic ovarian tumours whose features are not obviously those of another tumour type. A careful search for thyroid follicles should be undertaken. In problematic cases immunohistochemical staining for thyroglobulin may be required.
Antonio Ascenzi (1915-2000), a Pathologist devoted to Anthropology and Paleopathology

V. GIUFFRA, S. MINOZZI, S. MARINOZZI*, G. FORNACIARI

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Key words

Antonio Ascenzi • Anthropology • Neanderthals • Mummiology • Paleopathology

Summary

Antonio Ascenzi is well known within the scientific community for his original contributions to morbid anatomy and in particular for his studies on the fields of bone biology, bone biomechanics, haematology and congenital heart disease. Additionally, Ascenzi was also interested in human evolution and applied his deep knowledge of pathology to ancient human remains, conducting research in paleoanthropology on fossilized Neanderthal specimens found in Italy. The name of Ascenzi is linked with the discovery and study of the most ancient Italian bone fossils, namely the Ceprano skull, an early specimen of Homo erectus. Furthermore, his pioneering researches on the Uan Muhuggiag and Grottarossa mummies and his rigorous studies on several aspects and problems concerning the pathologies of past human populations made him a pioneer in the fields of Italian mummiology and paleopathology. The thread that linked his diversified research interests outside and within human anthropology was a profound passion for the search and discovery of scientific truth.

Introduction

Antonio Ascenzi was born on May 4, 1915 at Boulogne sur Mer, France. He obtained his degree cum laude in Medicine and Surgery at the “La Sapienza” University of Rome in 1940, discussing a thesis on the hypophyseal alterations secondary to leptomenigitis. During the Second World War, he took service as Medical Officer in Libya, an experience that he always remembered as one of the most important in his life, which profoundly affected his human and professional formation. After the war, Ascenzi started to work at the Institute of Pathological Anatomy, where he attained the position of Assistant Professor, and then of Tenured Assistant Professor University Lecturer, Senior Assistant Professor and finally, from 1957 to 1959, Professor “Incaricato” of the chair of Pathology (Morbid Anatomy). Starting in 1960 he held the same position at the University of Pisa, where he obtained the chair of Tenured Professor from 1963 to 1968 (Fig. 1). In 1968 he became Full Professor of the chair of Pathology (Morbid Anatomy) at the “La Sapienza” University of Rome where he continued and concluded his academic career.

Morbid Anatomy was Ascenzi’s main interest. The results of his original researches spanning from bone biology and bone biomechanics, to haematology and congenital heart diseases were published in prestigious national and international scientific journals. Alongside Morbid Anatomy, Ascenzi devoted himself to Paleoanthropology and Paleopathology. In early 1958, he became University Lecturer of Anthropology (Physical Anthropology) and, in 1961-1963, Professor “Incaricato” of Human Palaeontology at the “La Sapienza” University in Rome.

He was member of the Committee for Auxiliary Sciences of Archaeology of the National Research Council (CNR) from 1966 and President of the Italian Institute of Human Palaeontology from 1973. As a member of the Paleopathology Association, Ascenzi participated in several European Member Meetings 1-4. He was member of the Advisory Board of several scientific anthropological journals, including Rivista di Antropologia, L’Anthropologie (Paris), Bulletin et Mémoires de la

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In 1950, Ascenzi and Giovanni Lacchei made an important discovery. They brought to light another incomplete Neanderthal mandible (mandible III B) in the bone breccia alongside the entrance of the Guattari cave on Monte Circeo (Latium, Italy), where the remains of a skull (Circeo I) and a fragmented Neanderthal mandible (Circeo II, mandible A) were discovered in 1939. The mandible, estimated to belong to a male adult aged 18 to 20 years, was carefully studied. The results of the study were first published by Ascenzi and the anthropologist Sergio Sergi in 1955. The microscopic studies of Ascenzi on fossil bones continued on a specimen from the Neanderthal mandible “Circeo II A” observed by polarizing light microscopy and by electron microscopy on a number of animal specimens found in close proximity to the Neanderthal mandible “Circeo III B”. This research was the first to demonstrate the presence of histologically detectable organic matrix and the existence of a collagen component within the organic phase of a Neanderthal bone. Histologic methods and histochemical staining were established by this study as suitable techniques to verify the state of preservation of ossein in fossil bones. The aims of the microscopic investigations performed on prehistoric bones and the results reached until then, were summarized by Ascenzi in several papers.

In the meantime, the mandible of a Neanderthal child found at Archi (Calabria, Italy) in 1970 was studied by Ascenzi and the geologist Aldo Segre. The studies on Neanderthal remains were continued by Ascenzi with the analysis of the Circeo I skull, discovered by Alberto Carlo Blanc in the Guattari cave at Monte Circeo in 1939. The skull belonging to a male, aged 40 to 50 years, showed typical features of the European Homo Neandertalensis. In particular, Ascenzi and co-workers examined the irregularities of the palatal surface using histologic, microradiographic and electron microscopic techniques. The conclusion was that the Neanderthal man had a well developed torus palatinus of a nodular type, which was developing into the lobular type. Two years later Ascenzi edited the posthumous analytical work on the Circeo I skull (which Sergi had not been able to finish), by collecting the material, completing the unfinished observations of his colleague and providing a systematic draft of the work. The book was published by the Accademia Nazionale dei Lincei and represents a fundamental text on the subject and is accompanied by excellent iconography. For his contribution and life-long experience in Paleanthropology, Ascenzi was asked to write the contents for the entry “Man (Origin)” of the Italian Encyclopaedia Treccani.

Finally, the name of Ascenzi is strictly linked to another even more important discovery for Italian paleoanthropology. In 1994, during excavations for the construction of a highway near the town of Ceprano (Latium), a fossilized hominid calvarium of the Lower Pleistocene was brought to light. The calvarium, fragmented and incomplete, was estimated to belong to a strong young adult man. The specimen presented two pathological...
findings: a congenital malformation of the sphenoidal sinus, which was asymptomatic for the subject, and a healed depressed fracture of the right brow bridge, an injury probably caused by the attack of an animal 16-19. In 2000, a new reconstruction of the calvarium demonstrated that it could be classified as an early specimen of Homo erectus 20-22. The Ceprano skull represents the most ancient human fossil bone ever found in Italy and shows unique characteristics that contribute towards a better understanding of the history of human evolution.

Ascenzi: studies in Paleopathology

An innovative field of investigation pursued by Ascenzi is represented by bone alterations due to burial conditions. A first study on the state of preservation of skeletal remains immersed in sea-water for an extended period of time filled a gap due to the absolute lack of information at that time. The skeletal remains of three individuals dated back to the X century A. D. and found off the Mediterranean coast of France were analyzed to evaluate their state of preservation. Ascenzi and co-workers ascertained that the bones were quite well preserved, in particular the organic matrix, whose histological and histochemical properties were similar to those of fresh bones. In contrast, the inorganic component showed an increase, whereas the observed deterioration of the bones was attributed to the activity of micro-organisms 23.

Ascenzi dealt successfully with fundamental problems in paleopathology, such as the origin of thalassemia in Italy. Ascenzi carried out a wide survey of the Italian skeletal material with evidence of porotic hyperostosis, especially hyperostosis from southern sites. Because porotic hyperostosis occurs within a large group of haematologic disorders, and it is not only characteristic of thalassemia, he proposed rigorous criteria to formulate a diagnosis of the disease 24-26.

In a further study, Ascenzi provided evidence that haemoglobin can be quantitatively determined in ancient skeletal remains, even dating back to the Eneolytic age, using an immunochemical technique. Although haemoglobin had been shown to decrease with time, it was still found even in older specimens. This opened a new path to the solution of paleopathological problems, especially those on the origin of thalassemia 27.

Additional progress was made and recorded in a contribution presented in the volume of Ornert and Aufderheide 28. While a single macroscopic examination does not allow diagnosis of the aetiopathology of chronic anemias in skulls with evidence of porotic hyperostosis, the immunochemical technique was estimated to be sufficiently reliable to detect the content of haemoglobin traces in ancient bones. This represented a possible tool for an unequivocal diagnosis of alpha and beta thalassemia in skeletal remains, although a careful interpretation of these data is necessary 29.

Ascenzi was also interested in minor problems of Paleopathology. Some contributions summarized the value and results of modern medical techniques applied to paleopathology, such as regular light microscopy, electron microscopy 30 and histology of human bone remains 31.

Ascenzi: studies in experimental Archaeology

An interest that guided the researches of Ascenzi in Paleopathology was post mortem alterations of bone, by means of experimental archaeology. The first study was aimed at investigating the osteoclastic activity of fungi on buried bones. Fragments of human vertebrae obtained from fresh cadavers were buried in garden dirt for 45 days. Once exhumed, the histological preparations of the specimens were observed by electron microscopy, using fragments of the Circeo I skull for comparison. The fungal activity was represented by bone erosion, with resorption pits and boring channels; the degradation of crystallites and the organic matrix were similar between buried and fossil bones 32.

Experimental archaeology was also used to obtain information about the activity of micro-organisms on the above-mentioned bone immersed in Mediterranean Sea water. Ten specimens of fresh bone from bovine metatarsals were deposited on the seabed, at a depth of about 60 m. Every six months, two specimens were removed and observed by optical and electron microscopy. This research showed that micro-organisms that produce boring channels are amoeobic 33.

Ascenzi also used experimental archaeology to propose a provocative and fascinating interpretation of the artificial aperture in the occipital bone of Circeo I, already observed and commented by Sergi. Sergi had hypothesized that the opening in the skull had been artificially created in order to remove the encephalon. This conclusion was partially reached on the basis of the comparison with similar lesions found in crania belonging to Papuan tribes that practiced cannibalism. To verify this hypothesis, Ascenzi rehydrated a dry human cranium and reconstructed the stone tools used by the Circeo Neanderthals (pontinian type tools) to practice an artificial aperture in the occipital bone. The result, very similar to the original lesion, supported the hypothesis of an intentional opening of the Circeo I skull 34.

Ascenzi: studies in Mummmiology

The contribution of Ascenzi to Paleopathology is represented not only by the studies on fossilized and skeleton remains, but also on mummies in which soft tissues are preserved. During the winter of 1958-59, an archaeological expedition designed to survey the Tadrart Acacus in southern Libya explored a deposit under a natural shelter called Uan Muhuggiag, where the well preserved mummy of a child was discovered. The mummy was wrapped in an animal skin in an unusual position and
wore a shell necklace. Anthropological, radiological, histological and chemical analyses were performed under the direction of Ascenzi. It was ascertained that the mummy belonged to a 30-month-old child of undetermined sex with Negroid features. The mummification had been conducted first by evisceration, attested by a long incision of the abdominal wall, and then by natural desiccation. Furthermore, Ascenzi was involved in the study of a unique specimen, the so-called “mummy of Grottarossa”, discovered along the via Cassia in Rome in 1964. The body, belonging to an 8-year-old girl and dating back to the second half of the II century A.D., was buried in a marble sarcophagus. This is the only Roman example of mummification known to date. Ascenzi and his co-workers carried out an interdisciplinary project on the Grottarossa mummy, which involved traditional anthropological and paleopathological studies, as well as modern medical exams, such as X-ray of the teeth, CT scan imaging, sampling of tissues using CT-guided needle biopsies, regular light and electron microscopy, chemical analysis of embalming materials, pollen analysis, and study of textiles, jewelry and funerary items that accompanied the mummy. The results demonstrated that the body had been treated using a method typical of Egypt’s Roman Period. The body preserved brain and internal organs, showing that excerebration and evisceration had not been performed. The body and dressings were spread with resin, responsible for the brownish colour of the skin. No traces of natron or bitumen were detected. The paleopathological research showed that the girl had suffered from infection or malnutrition episodes, as evidenced by the Harris’ lines, from osteopenia, antracosis, and that she had died as a result of a bilateral fibrinous pleuritis of uncertain nature. The presence of textiles suggested that the mummification was performed in Italy following the Egyptian style.

The place of Ascenzi in Italian Anthropology and Paleopathology

For the fundamental nature of his contributions to the Italian Paleopathology, Ascenzi (Fig. 2) can be rightly considered the founder of modern Paleopathology as an autonomous discipline in Italy. Ascenzi was an eclectic researcher, a passionate experimenter and an illuminate teacher, who combined his profound knowledge of Morbid Anatomy to the study of the diseases in past populations. His interests in Paleopathology covered many fields, from osteoarchaeology to anthropology and mummiology. He applied the scientific method to the discipline rigorously, exploiting the medical techniques, such as radiology, electron microscopy, histology and histochemistry, in the study of ancient human remains. He did not hesitate to use experimental archaeology to explain certain phenomena and to obtain answers. We would like to conclude this tribute to Ascenzi by mentioning some aspects of his personality. He was a reserved person who detested adulation and was driven by a passion for search of scientific truth. He combined strong intuition and high rigor, which are crucial qualities for successful fundamental research. Additionally, his devotion and love for the work of the physician emerges from various episodes of his life. He felt that it was his duty as a physician to help the population of Albano Laziale where he resided during World War II. Working tirelessly, Ascenzi made up for the lack of medical assistance for many months, distinguishing himself for his spirit of abnegation and competence. In the years that followed, the City Council of Albano Laziale awarded him a gold medal for valor and freedom of the city, a recognition that he most appreciated.

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Expression of p16 in abnormal pap-tests as an indicator of CIN2+ lesions: a possible role in the low grade ASC/US and L/Sil (lg) cytologic lesions for screening prevention of uterine cervical tumours

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Key words
Expression of p16 • Progression factor • CIN2+ lesion indicator • Citologic lesions

Summary
The aim of this study was to assess the validity of protein p16 expression as an indicator of progression in lesions as ASC-US and L-SIL. For this purpose, we examined 246 cytological samples (91 ASC-US, 60 L-SIL, 36 ASC-H, 59 H-SIL) of which 151 were conventional Pap-tests (CC) and 95 in liquid based cytology (LBC) with colposcopic and histology follow-up. The results showed that in the positive p16 Pap-tests a 59% PPV vs CIN2+ in all cytologic diagnoses compared to 43% in cytologic reading alone. 96% of HG cytologic lesions were positive for p16, and the data showed good correlation between positivity for p16 in the cytologic preparations and the presence of CIN2+ lesions in the histologic test (chi-square for trend p < 0.0001). The sensitivity, specificity and NPV were 93%, 52% and 91%, respectively, in all cytologic diagnostic categories. P16 was positive in 46% of ASC-US and 53% of L-SIL. The PPV vs expressed CIN2+ was higher than that observed in cytologic reading (48% vs 26%, and 31% vs 20%, respectively). The sensitivity was 83%, the specificity 67% and 54%, respectively, and the VNP was 92% and 93%. It is possible to design algorithms for colposcopic follow-up that can reduce the need to obtain a follow-up. The future application of this test may allow the creation of a bio-molecular automated pap test.

Introduction
Uterine cervical cancer is the second most common form of cancer worldwide for incidence and mortality rates. Epidemiological and molecular studies have shown that 99.7% of cervical carcinomas harbour genomic sequences of Human Papiloma Virus (HPV) 1-2. It is well known that high oncogenic risk viral types (HR HPV) are responsible for integration of viral DNA within cellular DNA, leading to pre-neoplastic modifications that can regress, remain stable or progress to invasive tumours 3. However, most HPV infections are transitory, especially in young women 4, and only HR-HPV which actively expresses the oncoenic E6 and E7 proteins cause neoplastic transformation 3-5. The expression of viral oncoenes in proliferating cells interferes with the regulation of the cell cycle and lead to numerous biochemical interactions that result in changes of the expression profiles of many genes and/or proteins 6. These changes in the basal and parabasal layers of HR-HPV infected cells occur only rarely, and therefore the transformation process leading to carcinogenesis is only a very uncommon consequence of a very common infection. Numerous studies have led to the identification of a biomarker, protein p16^{ink4a} (p16) that can be detected by immunocytochemical methods 7. This marker is overexpressed in dysplastic cervical cells, and its overexpression is directly connected to a increased activity of the viral oncogene E7 8. The mechanism of p16 overexpression is largely well known, and it involves alteration of the cell cycle by the E7 oncogene with an increase in DNA synthesis and the blockage of cellular differentiation, which induces a higher probability of neoplastic transformation. In non-dysplastic cells, p16 is normally expressed at very low levels and cannot be detected by

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expression of p16 in abnormal Pap-tests as an indicator of CIN2+ lesions

The aim of the present study was to evaluate the over-expression of p16 in 246 abnormal Pap-tests obtained through a Cervical Carcinoma Screening Programme. The results were compared with those of colposcopies and biopsies, and the Positive Predictive Value (PPV), the Negative Predictive Value (NPV), Sensibility and the Specificity were calculated. We also examined the possible role of the immunocytochemical test for p16 in selecting women with low grade (LG) cytological lesions, such as ASC-US and L-SIL, to be subsequently submitted to colposcopy.

Materials and methods

Our Cytology Operative Unit (UOC) covers the provincial territory of Perugia, providing an active Screening Pap-test for three local health agencies (AUSL 1, 2 and 3) with an estimated population of 171,000 women between the ages of 25 to 64. Each year an average total of 50,000 cytological smears are carried out with approximately 2% abnormal pap-test results.

In this study we examined 246 cytological samples (91 ASC-US, 60 L-SIL, 36 ASC-H, 59 H-SIL) of which 151 were conventional Pap-tests (CC) and 95 were in liquid based cytology (LBC). Using either of 2 sampling methods, regarding evaluation of p16 immunocytochemistry, it has been suggested that 2 systems are equivalent to assess pre-neoplastic lesions of the cervix. Moreover, the “Recommendations for planning and execution of population screenings for prevention of uterine cervical cancer, breast cancer and colorectal cancer” - Italian Health Department, General Management of Prevention for cervical screening, state that the exam can be performed by conventional pap smear or by liquid based cytology (art. 2 bis L 138/2004 and National Planning of Prevention 2005/2007).

Samples were taken under colposcopy in screening-aged women (25/64) sent to level II after ASC+ alterations between the period from May 2007 to June 2008. 220 samples had colposcopic and histological follow-up, and 26 only colposcopic follow-up. The criterion for not performing biopsy was a negative colposcopy. We examined only 246 cytological samples because not all had follow-up, and not all material was received from abnormal cases.

Cervical-vaginal samples in LBC were taken using the ThinPrep system. The cytological classification used was the 2001 Bethesda system. The method used for the cytological sampling of p16 was set up in our laboratory and has been in use for several years.

Both CC and LBC Pap-tests are cytologically evaluated, mapped with a vitrographic pencil in those fields that contain morphologically significant cellular alterations. Unmasking of the epitope in the microwave after immersion in an antigen retrieval buffer pH 6.0 was performed for approximately 15 min. After unmasking, p16\textsuperscript{INK4a} primary antibody (Biocare Medical; 1/30 dilution for CC Pap-test and 1/100 for LBC Pap-test) was applied for 30 min to slides previously treated with peroxidase “block” to inhibit the endogenous peroxidase. Finally, the Novolink detection system kit (Novocastro) was used.

We employed the cytochemical coloration “i6000 GENOMIX” automatic instrument (Menarini Diagnostics). Papanicolau was used as contrast staining.

Results

The cytological observations of the “mapped” fields allowed us to evaluate the immunocytochemical reaction in morphologically altered cells thereby reducing the risk of false positives in metaplastic cells in the differentiation phase, as well as in cylindrical cells. Regarding the morphological aspect of the Pap-test, re-staining with the Papanicolau technique allows complex re-evaluation which is much easier than Harris’ haematoxylin (Figs.1-5). The use of a microwave oven to unmask the antigen proved to be a rapid and reliable method.

The reaction was considered positive if at least one atypical cell at immunocytochemical staining was contained within one of the mapped fields regardless whether the staining was only nuclear, only cytoplasmatic or both. 220 of 246 abnormal cytological samples underwent cytological testing and the remainder to colposcopic testing only. In this report PPV, NPV, sensitivity and specificity are calculated against CIN2+ lesions according to the indication of the screening.

Fig. 1. ASC-US: p16\textsuperscript{INK4a}+ intermediate atypical squamous cells and p16\textsuperscript{INK4a} - intermediate atypical squamous cells. Histology: CIN 1.
In all samples where histological diagnosis is the outcome, negative colposcopies were placed in the negative category.

Table I shows the distribution of histological diagnostic tests in the various cytological diagnostic categories. The PPV of cytological tests was 26% (24/91) for the ASC-US group; 20% (12/60) for L-SIL; 64% (23/35) for ASC-H and 78% (46/59) for H-SIL. The PPV referred to in all of the diagnostic categories was 43% (106/246).

Table II shows the correlation between the cytological categories and the reactivity for p16, which was positive in 45% (42/91) of ASC-US, 53% (32/60) of L-SIL, 97% (35/36) of ASC-H and in 95% (5/59) of H-SIL (chi-square for trend p < 0.0001). Overall, p16 was positive in 165 (67%) of the 246 Pap-tests studied.

Table III shows the distribution of histological diagnoses (also counting negative colposcopies among negative specimens) for various diagnostic categories and reactivity for p16.

Table IV, Comparison of the Positive Predictive Value (PPV) vs CIN2+ of cytology alone with respect to evaluation for p16 positivity.

In all samples where histological diagnosis is the outcome, negative colposcopies were placed in the negative category.

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Table III shows the distribution of histological diagnoses (also counting negative colposcopies among negative specimens) for various diagnostic categories and reactivity for p16.

Table IV also shows that the sensitivity of p16 towards CIN2+ lesions for the ASC-US category was 83% (20/24); 83% (10/12) for L-SIL; 96% (22/23) for ASC-H; 100% (46/46) for HSIL; and 93% (98/105) for all diagnostic categories.
The specificity of p16 was 67% (45/67) for ASC-US categories, 54% (26/48) for L-SIL and 52% for all diagnostic categories.

The NPV of p16 for ASC-US categories was 92% (45/49), 93% (26/28) for L-SIL and 91% (74/81) for all diagnostic categories.

In addition, the same correlation between the increase of positivity for p16 and the severity of cytological diagnoses (Tab. II) was found in histological diagnoses (Tab. III). The results were positive by immunocytochemical staining for p16 in 46% (25/56) of Pap-tests with a histological or colposcopic negative result, 48% (41/85) with a CIN 1 result, 89% (41/46) with CIN2 result and 97% (57/59) with CIN 3 (chi-square for trend p < 0.0001).

**Discussion**

In developed countries, organized screening programmes have reduced the incidence and mortality rate for cervical cancer. In the last decade, technological advances, both in sample collection and processing, have given an even greater value to screening programmes. In any case, to our knowledge, the Pap-test is a morphological test and as such presents some limits.

In this context, some authors have proposed the use of p16 overexpression as a marker for the presence and identification of high grade squamous epithelial lesions, also because this protein relates to active expression of the E6/E7 viral oncogenes and not with the sole presence of the virus.

The results obtained in our study confirmed the importance of a possible use for this marker in screening. In fact, 96% of ASC-H and HSIL cytological lesions were positive for p16. The number of p16 positive cases increased significantly with the increase in the
severity of the diagnostic category (chi-square for trend $p < 0.0001$) but, most remarkably, the results showed a good correlation between p16 positive tests in cytologic preparations and the presence of CIN2+ lesions in histological exams (chi-square for thread $p < 0.0001$).

Moreover, by comparing the results of follow-up, the PPV for CIN2+ lesions referred to all diagnostic categories of the immunocytochemical method was higher than conventional reading alone ($59\%$ vs $43\%$).

p16 protein was positive in 98 of 108 lesions found in the CIN2 and CIN3 histological control. p16 was negative in 5 cases with CIN2 histology and in 2 cases with CIN3 histology, distributed throughout all diagnostic categories, especially in ASC-US and L-SIL. The absence of p16 in 5 CIN2 cases can be explained with the significant possibility of a spontaneous regression of this lesion $^{16}$ and with the difficulty in histology to make it distinguishable from CIN1.

The 2 cases where the result was negative, 1 ASC-US and 1 ASC-H, with a CIN3 result in the histological exam, merit further attention. In re-examining the results of Pap-tests classified as ASC-US, only a few atypical cells were present ($<4$). This could have played a significant role in the failure to detect p16. In fact, as reported in the literature $^{17}$, not all atypical cells in a Pap-test are p16 positive. In the case of ASC-H $^{18}$, the absence of p16 in the presence of severe lesions may be explained by the lack of expression due to mutation of the p16 gene (deletions or hypermethylation of the promoter), as in cervical carcinogenesis, especially in women who are heavy smokers.

Of greater interest is the result of the test applied to the cytological evaluation of LG lesions such as ASC-US and L-SIL, which given their common characteristics, shall be discussed together in this section. As is well known, in fact, there are diagnostic categories with a high degree of inter-observer and disagreement with histological follow-up $^{19}$ associated with a low PPV. In organized screening programmes, the routine application of a diagnostic examination for LG cytological lesions by colposcopy can induce stress in women, apart from the extra costs that are not justified by results. A test that can predict severe histological lesions in the presence of atypical cytological LG’s could be quite useful. Considering the data obtained, p16 appears to be the ideal test for this purpose. In fact, the PPV vs CIN2+ for this category of p16 positive Pap-tests was significantly higher compared with the PPV obtained for the same diagnostic categories from cytological reading alone (PPV $41\%$ vs $24\% = p < 0.05$). The sensitivity of the test vs CIN2+ was $83\%$, the specificity was $63\%$ and the NPV was $92\%$. The 6 cases with a negative p16 and a CIN 2+ histological exam have already been discussed in detail (5 CIN2 and 1 CIN3).

In addition, the $93\%$ (98/105) sensibility results, with $52\%$ specificity and $59\%$ PPV obtained by using the p16 test on abnormal Pap-tests inclusive of all diagnostic categories, lead us to believe that p16 may be useful as a primary screening test. The hypothesis of direct immunological staining of the Pap-tests and subsequent automated reading could open the way to automation of biomolecular Pap-test. It is also useful in this regard to consider that a immunocytochemical test is easy to perform and has a relatively low cost compared to other bio-molecular methods.

References


ABBREVIATIONS
CC = Pap-test with Conventional Cytology
LBC = Pap-test with Thin-Layer, Liquid Base Cytology
HPV = Human Papilloma Virus
HPV HR = High Risk Human Papilloma Virus
ASC-US = Intraepithelial Squamous Lesions of Unknown Significance
ASC-H = Intraepithelial Squamous Lesions of Unknown Significance (not excluding High Grade Lesions)
L-SIL = Low Grade Squamous Intraepithelial Lesions
H-SIL = High Grade Squamous Intraepithelial Lesions
CIN = Cervical Intraepithelial Neoplasia
LG = Low Grade Lesions
HG = High Grade Lesions
PPV = Positive Predictive Value
NVP = Negative Predictive Value
Pathologic examination and staging of rectal carcinoma: a critical review

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Key words
Cancer • Rectum • Review • Pathological examination • Staging

Summary
In rectal carcinoma, accurate pathological examination is crucial for a correct staging and identification of predictors of risk of both local recurrence and overall survival. Accordingly, surgical pathologists determine many facets of rectal carcinoma patient care. Although rectal carcinoma shares many pathologic features with colon carcinoma, however, the anatomical location of the rectum poses additional problems in formulation of a pathological report. The most critical issues of pathological examination in rectal carcinoma involve assessment of: i) surgical resection margins (distal and circumferential resection margins); ii) total mesorectal excision (the plane of surgery); iii) peritoneal serosa involvement; iv) distance of invasion beyond the muscularis propria; v) number of lymph nodes to be recovered; vi) mesorectal tumor deposits; and vii) histologic regression grade after preoperative chemoradiotherapy. Although seemingly straightforward, the definition and macroscopic/microscopic interpretation of these key pathological features are still controversial, and lead to pathological reports that are variable not only among the different institutions but even within a single institution. The aim of this critical review on rectal carcinoma is to discuss confusing and/or challenging pathological problems, especially those with clinical impact, in order to provide a checklist that is useful for practicing surgical pathologists.

Introduction
Currently, there is increasing recognition of the importance of the surgical pathologist in the management of rectal cancer, especially since therapeutic options adopted by oncologists are largely guided by the pathological report. The skill of the pathologist includes an adequate sampling of the surgical specimen and formulating a correct histological diagnosis that will provide clinically useful prognostic information. Guidelines for reporting of rectal carcinoma are usually included in those of colon carcinoma. Although rectal and colon carcinomas share common controversial pathological issues, concerning tumor staging (number of lymph nodes to be recovered; interpretation and inclusion of perivisceral tumor deposits in TNM; interpretation and reporting of tumor budding), rectal carcinoma poses exclusive issues, owing to its peculiar anatomical location. In fact, the pathologist should be aware of rectal and mesorectum anatomy for assessing: i) gross evaluation of the total mesorectal excision; ii) possible extension of tumor to the surgically created circumferential (radial) margin; iii) possible extension to peritoneum, if tumor is localized in the anterior wall of the rectum; and iv) assessment of tumor regression and pathological TNM stage in patients treated with preoperative radiochemotherapy (neoadjuvant therapy). The authors present a critical review on the reporting of rectal carcinoma, with no intention to constitute either a protocol or guidelines for this tumor. The aim is to offer pathologist a practical approach when faced with gross and histological examination of surgically-removed specimens of rectal carcinoma. In this regard, the most relevant issues will be discussed and macroscopic and microscopic illustrations, taken from the personal archives of the authors, are provided. Based on a review of the literature and our own personal experience, a checklist of rectal cancer, containing the most clinically relevant pathological features, is provided to assist the pathologist in reporting final diagnosis. It should be noted that the use of the present checklist other than for the above mentioned purpose is beyond its intended scope.

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We believe that this checklist may be extremely helpful, especially for pathologists who do not work within a specialized multidisciplinary team for colorectal cancer.

**Gross examination**

**Assessment of Total Mesorectal Excision (the plane of surgery)**

Mesorectal excision is a surgical technique involving complete removal of the intact mesorectum including the lymphatics, lymph nodes, nerves, and vascular supply. This evaluation, consisting of visual inspection of the removed rectum, allows the pathologist to judge the completeness on surgical resection specimen, identifying defects and irregularities in the mesorectum. This assessment is achieved by applying the following 3-tiered grading system: i) complete resection (mesorectal plane of surgery); ii) nearly complete resection (intramesorectal plane of surgery); iii) incomplete resection (muscularis propria plane of surgery). A “complete resection” is obtained if surgically resected mesorectum is intact, with only minor irregularities (i.e., no defect is deeper than 5 mm) on its external surface and with a smooth circumferential margin on slicing. In addition, there may be no coning toward distal margin of the specimen. A “nearly complete resection” refers to a moderate bulk to mesorectum, with irregularities greater than 5 mm of the surface and circumferential margin on slicing, but with no extension to the muscularis propria. An “incomplete resection” refers to little bulk to mesorectum with defects down onto the muscularis propria (Fig. 1) and/or very irregular circumferential margin on slicing.

The completeness of mesorectum resection (mesorectal plane of surgery) is an independent prognostic factor for local recurrence. After complete resection and 3-tiered grading system, we have twice the rate of local recurrence (44% vs 27% for complete resections) also because patients with negative margins, but with an incomplete mesorectal resection, have twice the rate of overall local recurrence. In addition, there is evidence that complete mesorectal resection improves local recurrence rates and corresponding survival by as much as 20%.

**Tumor site**

It is crucial that the surgical specimen is correctly oriented to establish if tumor is localized in the anterior or posterior wall of the rectum and if it is above, at or below the peritoneal reflection. This is extremely important because carcinomas located in the anterior rectal wall, above peritoneal reflection, extend to the peritoneal serosa. In contrast, tumors of the anterior rectal wall located below the peritoneal reflection and tumors of the posterior rectal wall usually infiltrate the mesorectum (circumferential resection margin).

**Distance of Tumor to Distal Margin**

This issue is especially important when the pathologist is dealing with a carcinoma of the lower rectum. It is prognostically important that distal resection margin of the resected specimen is within 1 cm of the resection site. The significance of the distal margin is based on the consideration of the surgical plane of resection. The radial margin is a surgically created margin produced during removal of the rectum from its surroundings. A full 360° CRM is present only below the peritoneal reflection, while its corresponding outer layer of excised mesorectum above the peritoneal reflection. The standard for macroscopic assessment of CRM is that first reported by Quirke and later modified. Briefly, it consists of complete transverse slicing of the entire tumor and the surrounding mesorectum from the mucosal aspect, at 3-5 mm intervals. Slicing should be extended for 2 cm above and below the tumor. The pathologist should look for continuous tumor spread to the CRM, reporting the distance from tumor to the nearest margin. If tumor is near or at margin, it should be sampled en-bloc with the resection margin.

**Assessment of Circumferential Resection Margin**

Circumferential resection margin (CRM), also known as “radial margin”, is a surgically created margin produced during removal of the rectum from its surroundings. A full 360° CRM is present only below the peritoneal reflection, while it corresponds to the outer layer of excised mesorectum above the peritoneal reflection. The gold standard for macroscopic assessment of CRM is that first reported by Quirke and later modified. Briefly, it consists of complete transverse slicing of the entire tumor and the surrounding mesorectum from the mucosal aspect, at 3-5 mm intervals. Slicing should be extended for 2 cm above and below the tumor. The pathologist should look for continuous tumor spread to the CRM, reporting the distance from tumor to the nearest margin. If tumor is near or at margin, it should be sampled en-bloc with the resection margin.
Although one block may be sufficient, up to six blocks may be necessary to a complete assessment of margin involvement, especially in those cases with extensive tumor spread into perirectal fat (Fig. 3). In addition, the pathologist should accurately look for the presence of discontinuous tumor deposits or metastatic lymph nodes in perirectal fat, measuring the distance between them and the nearest CRM. Both tumor deposits and lymph node metastases at or near the margin should be sampled en-bloc with the resection margin. Although the method of Quirke is widely used, it cannot be ignored that taking several blocks to establish the relationship of the tumor to the mesorectal surgical margins may potentially compromise the assessment of local lymph nodes. Accordingly, we suggest using the method of Quirke when tumor is macroscopically at the margin or very close to it as detected by manual palpation. Alternatively, CRM can be evaluated by sampling, into multiple blocks, a 1 mm slice of adipose tissue from the whole external surface of this margin (Fig. 4). This latter method has the advantage of keeping perirectal adipose tissue intact so that lymph nodes can be retrieved and counted in simpler manner.

**Assessment of Peritoneal Serosa Involvement/Perforation**

Serosal tumor involvement is a prognostically adverse feature for local recurrence. Surgical specimens from patients with rectal cancer located in the anterior surface at or above the peritoneal reflection should be assessed carefully to establish its relationships to peritoneal serosa involvement/perforation.
toneal serosa (i.e., grossly normal or retracted serosa; macroscopic perforation). Accordingly, the pathologist should perform an adequate sampling (at least two blocks) of tumor area closest to peritoneal serosa. Perforation due to tumor wall invasion is uncommon in rectal carcinoma, but when present is associated not only with poor prognosis but also with high in-hospital morbidity and mortality.

**NUMBER OF LYMPH NODES TO BE RECOVERED**

Several studies have demonstrated that N stage is an independent risk factor for local recurrence and overall survival for patients undergoing curative resection. Lymph node status has also been demonstrated to be the strongest prognostic factor in patients with locally advanced rectal cancer treated with preoperative chemoradiotherapy. Accordingly, a careful search for lymph nodes, including those measuring less than 5 mm in diameter, is crucial for correct staging, prognostic information and therapy for patients with rectal carcinoma. All lymph nodes recovered must be submitted entirely for histology, unless they are of a large size. In this case, grossly serial sectioning and submission of all slices for histological examination is recommended. Histological examination of multiple tissue levels is currently considered as optional, with one tissue level the minimum requirement.

It has been widely demonstrated that the number of lymph nodes analyzed is itself an independent prognostic indicator in colorectal cancer, as suggested by the evidence that overall survival is significantly worse in patients in which a small number of lymph nodes (<7 to 9) have been found. Based on these findings, some authors state that a large number of patients with colorectal cancer are staged inadequately. This is supported by the evidence that oncologists recommend adjuvant therapy for patients who are staged pT3N0, but with only a few lymph nodes retrieved. The minimum number of lymph nodes to be recovered is still matter of debate, but it should be stressed that an ideal number does not exist, being only a statistical concept that cannot be applied to each single patient. Currently, many authors, as well as the tumor-node-metastasis (TNM) system, recommend that a minimum number of 12 to 18 lymph nodes per specimen is acceptable for accurate prediction of regional node negativity. Other studies have demonstrated that more than 20 lymph nodes are necessary for more accurate prognostic stratification. Therefore, re-examination of residual perirectal adipose tissue is strongly recommended if less than 12 lymph nodes are found because there is a risk that small lymph node metastases (less than 5 mm in size) might have been missed. However, apart from diligence and skill of the pathologist, it should be underlined that the number of lymph nodes recovered in a single surgical specimen greatly varies and largely depends on multiple factors, including variation in patient anatomy, obesity, quality of surgical excision, tumor stage, tumor-associated inflammatory response, and preoperative neoadjuvant therapy. Thus, the recovery of only a few lymph nodes in a single surgical specimen does not necessarily imply that sampling by the pathologist has been insufficient. However, it is currently accepted that pathologists should be able to find routinely an average of 15-21 lymph nodes to confirm adequate dissection practice.

In daily routine, the final recommendation is that as many lymph nodes as possible should be retrieved, even if 12 lymph nodes have been found. This suggestion is based on the evidence that the chance of diagnosing metastases increases when a greater number of lymph nodes are examined and that a significant number (17-30%) of pT3N+ patients have only a single metastatic lymph node. In addition, the number of lymph nodes retrieved also seems to be important in N+ patients, because two recent studies have demonstrated that the ratio of metastatic lymph nodes to the overall number of lymph nodes recovered is strongly correlated with the 5-year survival rate. Importantly, it should be stressed that the pathologist should pay particular attention to searching for small-sized (<5 mm) lymph nodes, because a significant number of metastases can be demonstrated within these. Histological examination of these lymph nodes is crucial to avoid potential understaging, especially in pT3 patients. As these small lymph nodes can be easily missed or crushed during sampling, the pathologist should search for them with diligence.

Lastly, it should be remembered that lymph nodes may shrink after preoperative chemoradiotherapy, rendering their identification more difficult. Accordingly, the mean number of lymph nodes recovered, including those metastatic, is decreased in rectal cancer treated with neoadjuvant therapy when compared to surgery alone, despite an extensive search. In this context, even the mean size of the largest lymph node found is lower (4 mm) when compared with the diameter (7 mm) seen in a surgical specimen that has not been preoperatively treated. This suggests that multiple blocks of mesorectal fat should be processed before reporting a ypNo category. Although it is likely that the greater the number of lymph nodes detected, the greater the chance that metastasis will be found, two recent studies have shown that survival and local recurrence do not seem to be influenced by the number of lymph nodes retrieved in rectal carcinoma treated with chemoradiotherapy.

**Histological examination**

**TUMOR HISTOTYPES**

The following distinctive histotypes are currently recognized by WHO: i) adenocarcinoma not otherwise specified (N.O.S.); ii) mucinous (colloid) adenocarcinoma; iii) signet-ring cell carcinoma; iv) squamous cell carcinoma; v) adenosquamous carcinoma; vi) medullary carcinoma; vii) small cell carcinoma (high-grade...
neuroendocrine carcinoma); viii) undifferentiated carcinoma.

Some of these histotypes, including mucinous, signet ring cell, and medullary carcinomas, deserve a detailed comment. According to the WHO classification, only tumors with more than 50% of extracellular mucin secretion should be defined as “mucinous carcinoma”. Although mucinous carcinoma is graded in the WHO classification, by convention, as a high grade tumor, some authors recommend to grade mucinous carcinomas into low or high grade for prognostic purposes. A tumor is defined as “signet-ring cell carcinoma” if more than 50% of neoplastic cells have intracytoplasmic mucin and nuclei displaced at the periphery, imparting a signet-ring morphology. Signet ring cell carcinoma, along with small cell and undifferentiated carcinomas, are non-gland-forming tumors, and thus classified by convention as high grade. Medullary carcinoma is typically a well circumscribed tumor, characterized by a proliferation of cells with abundant eosinophilic cytoplasm, vesicular nucleus containing a prominent nucleolus, usually arranged in nests, or organoid/trabecular solid growth pattern. Another distinctive feature is the presence of numerous lymphocytes infiltrating tumor. Recognition of mucinous, signet ring, and medullary carcinomas is important because these tumors can be associated with high levels of microsatellite instability (MSI-H). Therefore, their identification may be potentially useful in terms of a prognostic marker of outcome, predictive marker of response to chemotherapy, and, lastly, as a screening tool for hereditary nonpolyposis colon cancer (HNPCC; Lynch syndrome).

**TUMOR GRADE**

Multivariate analyses have shown that tumor grade is a stage-independent prognostic factor. Unfortunately, although several different grading systems have been proposed, there is no general consensus among pathologists in adopting a single, widely accepted and uniformly used grading system. Based on the percentage of gland-like structures formed by the tumor, the WHO classification recognizes 4 grades: (i) well differentiated-G1 (glands > 95%); (ii) moderately differentiated-G2 (glands among 50-95%); (iii) poorly differentiated-G3 (glands among 5-50%); and iv) undifferentiated-G4 (glands < 5%). Although seemingly straightforward, there is a significant degree of inter-observer variability, especially when evaluating well (G1) vs moderately (G2) and moderately (G2) vs poorly (G3) differentiated carcinoma. A 2-tiered grading system, low grade and high grade, based exclusively on the amount of gland formation (low grade, ≥ 50% gland formation; high grade, < 50% gland formation), has been proven to be prognostically useful and is equally acceptable. Although some authors recommend that tumor grading should be based on morphological features of the predominant area, others state that tumor should be graded on the worst area present, even if it is not predominant. In this regard, the presence of tumor budding and/or leading front of invasion with dedifferentiation should not be considered as the worst tumor component.

Recently, some authors have proposed a 3-tiered grading system, based on the extent of the poorly differentiated component, defined as a tumor area showing no glandular formation. In this study, grade III was applied to those tumors for which the poorly differentiated component fully occupies the microscopic field of a 40 x objective lens.

**LOCAL PERITONEAL INVOLVEMENT**

Histological assessment of tumor extension to the peritoneal surface (pT4) has prognostic significance, especially in terms of local (pelvic) recurrence but also overall survival. Multiple sections should be cut from those blocks where tumor is closest to peritoneal surface, in order to ascertain their relationships. Histologically, local peritoneal involvement (LPI) is divided in the following four groups: (i) LPI-1: peritoneal involvement absent; (2) LPI-2: mesothelial inflammatory and/or hyperplastic reaction with tumor close to, but not present at the peritoneal surface (pT3); (3) LPI-3: peritoneal surface unequivocally infiltrated (pT4); (4) LPI-4: peritoneal involvement with ulceration and tumor cells lying free in the peritoneal cavity (pT4) (Fig. 5).

LPI2 group deserves a separate comment. In this regard, some authors have emphasized the possibility that some tumors, which extend very close (within 1 mm) to the peritoneal surface and with an associated fibro-inflammatory reaction and partial or complete loss of overlying mesothelium, could have previously breached the mesothelium, even if no tumor cells can be identified at the peritoneal surface. This is supported by the evidence that in some cases, by applying elastic staining, destruction of the peritoneal elastic lamina can be observed. Therefore, we agree with those authors who recommend to report if tumor is within 1 mm of the peritoneal surface, because the possibility of transperitoneal tumor spread cannot be completely ruled out. In these cases, although tumor stage remains pT3, oncologist should carefully...
evaluate this information in pT3N0 patients in order to decide if adjuvant therapy should be administered. As serosal involvement has been documented in 25.8% of rectal cancer specimens, the pathologist should accurately search for LPI because it is likely under-reported in daily practice. This is supported by the evidence that serosal involvement (LPI3-LPI4) could be identified in 22% of cases, initially diagnosed as negative, after a meticulous revision of original histological slides. Although LPI-3 and LPI-4 are grouped together into pT4 category of TNM7, their separation is justified because LPI-4 is currently believed to be more reliable for predicting pelvic recurrence and/or persistence than LPI-3.

Some authors propose substaging T4 into T4a (tumor invasion into adjacent organs) and T4b (tumor extension to serosa). This distinction is based on data showing that serosal involvement seems to have a particularly poor prognosis compared with invasion of adjacent organs. However, in TNM7, it has been proposed that the T4 subsets be reversed (i.e. T4a invasion of peritoneum; T4b invasion of adjacent organs), because serosal involvement has a 10% to 20% better 5-year survival than local invasive carcinoma for each category of N stage.

**DISTANCE OF INVASION BEYOND THE MUSCULARIS PROPRIA**

Although several studies have shown that the extent of mesorectal invasion is a prognostic indicator in pT3 colorectal carcinoma, these data have not been confirmed by other authors. These discrepancies may be partly due to different cut-offs (< 1, 3, 4, and 5 mm) assigned by several authors, and difficulties in measuring tumor extension in those cases in which the muscular wall was largely destroyed by the tumor. In one study, it was demonstrated that the distinction of pT3 carcinomas into minimally invasive (fat invasion detected only on histological examination) or advanced tumors (fat invasion evident on macroscopic examination) has a strong prognostic significance in terms of local recurrence (5.4% vs 14.2%). The potential adoption of this classification (minimally invasive vs advanced) seems to be supported by a recent study showing that patients with a distance of invasion < 1 mm have better 5-year survival (60.8% vs 36.9%) compared to a distance greater than 15 mm. Therefore, we agree with authors who recommend to report the distance of invasion beyond the muscularis propria whenever possible.

**CIRCUMFERENTIAL RESECTION MARGIN INVOLVEMENT**

Tumor involvement of CRM is the most important risk factor of local recurrence and a strong predictor of survival. The status of CRM has predictive value even after neoadjuvant therapy. It has been calculated that a positive CRM increases the risk of recurrence and death from disease by 3.5 and 2-fold, respectively. However, although a recent study confirms both the high rate of local recurrence and poor survival in patients with CRM positive tumors, in multivariate analyses margin status was not an independent risk factor of local recurrence. The status of CRM is evaluated by measurement of the distance from the tumor to the nearest margin. Based on clinical trials, CRM is considered as negative (tumor-free) if the distance from tumor to the nearest margin surface is more than 1 mm, whereas it is positive if ≤ 1 mm (from 0 to 1 mm). Recently, it has been proposed that patients with positive CRM should be subclassified into two categories: i) tumor directly at the resection margin; ii) minimal distance between tumor and the CRM of ≤ 1 mm. This proposal classification has a prognostic value since the 5-year local recurrence rate after radical surgery is 55% vs 28%, respectively, if tumor is at the margin (R1 of the TNM residual tumor classification) or the tumor distance from the margin is ≤ 1 mm. In the latter case, it should be emphasized that the prognostic value is significant if all other resection margins are intended to be negative (i.e., R0 of the TNM residual tumor classification). However, some authors have shown that a CRM of ≤ 2 mm confers poorer prognosis, suggesting that not one millimeter but two millimeters is the limit that better predicts local recurrence. Given these conflicting results, we suggest reporting CRM as “positive” only if tumor margin, and specifying the distance between tumour and margin in patients with negative margins. It is noteworthy that at least six different types of tumor involvement of the CRM can be detected: i) direct tumor spread; ii) discontinuous tumor spread; iii) lymph node metastasis; iv) vascular invasion; v) lymphatic invasion; and vi) perineural tumor spread. Interestingly, it has been shown that there is a significant association with an increased rate of local recurrence, especially when the margin is involved by direct tumor spread and/or lymphatic invasion, followed by perineural, discontinuous tumor spread, vascular invasion and, lastly, by lymph node metastasis. Accordingly, when reporting a positive tumor margin, the pathologist should specify the type of tumor involvement as described above.

**LYMPH NODE MICROMETASTASIS AND ISOLATED TUMOR CELLS**

Currently, there is insufficient data to recommend the routine examination of multiple tissue levels from paraffin blocks and/or the use of ancillary techniques (i.e., immunohistochemistry, PCR) to improve detection of micrometastases (aggregation of tumor cells measuring 0.2 to 2 mm in size) or isolated tumor cells (single focus of a few tumor cells in a single node, or multiple foci of a few tumor cells within a single or multiple nodes, with an overall size ≤ 0.2 mm). This is mainly due to the fact that, albeit isolated tumor cells and/or micrometastases have been reported in many studies, their prognostic value still remains to be established because conflicting data have been obtained. Irrespective of prognostic significance, however, the detection of micrometastases should be reported as pN1(mi), and
isolated tumor cells as pN0(i+), if both have been detected at a morphological level alone or in combination with immunohistochemistry.

**Mesorectal Tumor Deposits**

Tumor deposits (TDs) are macroscopic and/or microscopic metastatic foci of variable size (ranging from < 1 mm to > 10 mm) within perirectal fibroadipose tissue, which are not associated with a recognizable lymph node structure and are not contiguous with the mural component of invasive carcinoma. Notably, they are usually found in locally advanced cancer specimens, and frequently sampled and submitted by the pathologist as lymph nodes. Several studies have shown that the presence of colorectal TDs is associated with poor prognosis in terms of both local and distant recurrence. In addition, their presence seems to have worse prognostic significance than lymph node metastases and may be associated with shorter survival in patients with coexisting lymph node metastases. In rectal cancer, their reported incidence varies widely, from 4.5% to 45% of cases. Most TDs have been detected in the mesorectum of lower rectal cancers, with a significant percentage (25-38%) detectable in the outer layer of the mesorectum. Therefore, these findings suggest that a complete mesorectal excision is crucial for their identification.

Histologically, TDs are quite heterogeneous in composition, appearing as rounded and/or irregularly shaped lesions, variably associated with small aggregates of lymphatic tissue that is not organized in lymph nodes, large vessels and/or nerves. Their origin and nature are still controversial. Although there is the tendency to regard TDs as growing metastases in perirectal fat, resulting from tumor spread along lymphatic/vascular structures and nerves, it is likely that, at least some TDs with smooth contours, actually represent completely metastatic lymph nodes.

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Although there is the tendency to regard TDs as growing metastases in perirectal fat, resulting from tumor spread along lymphatic/vascular structures and nerves, it is likely that, at least some TDs with smooth contours, actually represent completely metastatic lymph nodes. In addition, there is the possibility that some TDs, especially those found near the intestinal wall, could be the result of a finger-like extension into fat by the primary tumor, which cannot be demonstrated in the area sampled. This uncertainty has generated confusion when interpreting TDs as a factor in determining tumor stage (TNM). According to TNM5, any perirectal TD should be classified as lymph node metastasis if its size is > 3 mm, whereas it is included in the T category (T3), namely, regarded as a discontinuous tumor extension, if it is ≤ 3 mm. However, TNM6 recommends that TDs with a form and smooth rounded contour of lymph nodes should be classified as lymph node metastases, whereas those with irregular contours are defined as venous invasion and included in the T category. Both TNM5 and TNM6 have been subjected to multiple criticisms by several authors. The major criticism of TNM6 involves the definition of rounded versus irregularly shaped TDs and in interpreting extramural tumor nodules with irregular contours as venous invasion, without any morphologically proven evidence. Although seemingly straightforward, there may be poor reproducibility among pathologists in determining the shape (round vs irregular), since some TDs may simultaneously show a partial rounded-shaped contour and a finger-like extension into fat. However, in our opinion, the proposal of replacing TNM6 with TNM5 as suggested by some authors does not resolve the problem, because there is no convincing evidence that TDs measuring more than 3 mm really represent lymph node metastases upon systemic sectioning. Therefore, there is the risk that the N-stage depends largely on the personal decision of pathologists to adhere to TNM5 or TNM6.
transit-metastasis with a high risk for local and systemic recurrence. We do not agree in reporting the presence of neoplastic foci entirely confined exclusively to a vascular (lymphatic or venous) wall as TD (intravascular TD), because the main characteristic feature of TD, i.e., perivascular fibroadipose tissue invasion, is absent. If we accept to include lymphovascular invasion alone (i.e., without association with fat invasion) in the category of TDs, extramural lymphatic and venous invasion should not appear on the pathology report. Nonetheless, we prefer to maintain extramural lympho-vascular invasion separately from TDs, especially because extramural venous invasion has an independent prognostic significance for survival and can be detected even if not associated with TDs.

Based on the results of a meta-analysis involving 3714 patients from several studies in the literature, 18% of cases had a combination of TDs and lymph node metastases, whereas in 8% of cases TDs were present without lymph node metastases. In patients with a combination of TDs and lymph node metastases, there was no impact on treatment as these patients are candidates for adjuvant chemotherapy. However, in patients with TDs alone problems in terms of staging and treatment may arise. In the latest edition of TNM (TNM7) TDs, irrespective of their number, size, and histology, are included in the N category (N1c), if such deposits are seen in tumors that would otherwise be classified as T1 or T2. In addition, it is also stated that “if a nodule is considered by the pathologist to be a completely replaced lymph node (generally having a smooth contour), it should be recorded as a positive lymph node”. In practice, this implies that patients with stage II disease in whom any TD is identified, are included in stage III, and are therefore candidates for adjuvant chemotherapy. Unfortunately, it is not yet clear if in N+ patients the number, size and morphology of TDs may play a negative prognostic role. In addition, there is still no general consensus about interpretation of TDs in patients undergoing neoadjuvant therapy. In fact, in these patients extensive tumor regression may lead to isolated tumor foci in the mesorectum that are morphologically similar to TDs. It is likely that these neoplastic foci are a sign of tumor regression, and therefore we agree with authors who recommend that these lesions should not be classified as TDs but as residual microfoci ypT3 to avoid upstaging and overtreatment.

Despite the fact that reproducible histological classification of TDs still must be established, in daily practice we feel it is worthwhile to include them in the pathology report, specifying, whenever possible, their total number, size (the largest diameter if multiple lesions), and association or not with large vessels and/or nerves. Further studies are needed to classify TDs with more reproducibility in order to create more homogeneous groups of patients for enrolment in clinical trials. This is crucial to better define the actual prevalence and clinical implications of TDs.

Vascular (lymphatic and venous) invasion

The presence of lymphatic invasion has been reported to be an independent prognostic indicator for survival in colorectal cancer. However, disparate results have been obtained, making it extremely difficult to draw definitive conclusions. This difficulty is partly due to interobserver variation among pathologists in defining “lymphatic invasion”. (i) tumor cells within a space lined by endothelial cells; (ii) tumor cells attached to the vascular wall; (iii) lymphatic vessels interrupted by tumor cells. In addition, it is well known that artefacts (i.e. retraction artefact and/or knife carryover artefact) may mimic “true vascular invasion”. and that distinction of lymphatic vessels from post-capillary venules is difficult as they are small and thin-walled structures. In contrast, several studies have shown that extramural, more than intramural, venous invasion is a risk factor for liver metastasis and a strong stage-independent adverse prognostic factor. However, identification of venous invasion is not always straightforward on histological examination. Indeed, destruction of vessel walls by tumor cells may completely obscure the pre-existing blood vessel. In this regard, some studies have emphasized the possibility of increasing the detection of venous invasion by routinely performing elastin staining. Interestingly, a recent study has underlined that interobserver agreement among gastrointestinal pathologists, not only for lymphatic but also for small and large vessel invasion, was fair and not improved by use of immunohistochemical stain. This disagreement was mainly due to the different criteria of “vascular invasion” adopted by different pathologists: (i) identification of a muscular wall adjacent to tumor; (ii) tumor invasion and disruption of a muscular wall; (iii) tumor present within a vein; (iv) identification of an elastic lamina (intact or disrupted) surrounding tumor focus, as feature of a pre-existing blood vessel obliterated by tumor. Lastly, the poor reproducibility of extramural venous invasion (EVI) may be partly explained by the different number of tumor blocks taken in different institutions. It has been calculated that the detection of EVI increases proportionally if the number of tumor blocks varies from 2 to 5 (59% vs 96%) is 104.

Although we are aware that neither expertise nor the routine use of special (histochemical and/or immunohistochemical) stains will entirely avoid observer variation, the pathologist should nonetheless accurately search for EVI since it may be under-recognized in daily practice. This is supported by evidence that EVI can be identified in 15% of cases, initially diagnosed as negative, after meticulous revision of original histological slides. This identification is not merely of academic interest as it may be a poor prognostic factor. At present, there are neither widely accepted guidelines nor minimal criteria for pathologic evaluation of lymphovascular invasion. However, it is largely accepted that venous, especially EVI, more than lymphatic invasion, has adverse prognostic significance. Accordingly, we suggest, in agreement with other
authors, that only EVI, specifying if macroscopically or microscopically detected, should be included in the pathology report. EVI should be diagnosed only when tumor is unequivocally confined within thick-walled veins (Fig. 8). Lymphatic and intramural venous invasion are actually considered to be optional parameters in the final report of colorectal carcinoma 5 6.

**Tumor Budding**

Several studies have demonstrated that the presence of high levels of tumor budding has an adverse impact on overall prognosis of colorectal cancer 131-133. Unfortunately, there is no general consensus about the definition and quantification of tumor budding 31. While some authors regard tumour budding as single isolated cancer cells or a cluster composed of 4 cells at the invasive tumor front 5, others include in the definition a cluster composed of 5 cells or even generic small clusters (number of cells not established) of undifferentiated cancer cells, also known as solitary trabecular forms 133. In addition, there is no reliable method of quantifying tumor budding as low vs high 31. A recent study has proposed an apparently reproducible, rapid and prognostically significant budding scoring system 134. A tumor bud was defined as single or as a group of < 5 detached tumor cells, usually but not always at the invasive front (Fig. 9). Tumor slides are initially scanned at low magnification, searching for areas with the highest density of tumor budding. For those cases in which tumor budding cannot be observed by scanning, the score will be performed on randomly selected areas from the slide. The method consists in evaluating three slides per tumor, examining 5 different areas at 200x magnification for each slide. Each area is considered positive if ≥ 1 bud is present or negative if no buds can be detected. The number of tumor budding for each area is reported (i.e., 0,1,2,3,4,5), so that 15 budding scores (15 numbers) will be available for 3 slides. If at least 50% of areas examined are positive for tumor budding, the case is classified as “high budding”; conversely, cases are categorized as “low budding” if less than 50% of areas examined are positive. In that study, budding was demonstrated to be present in tumors with either infiltrative or expansile margins (Fig. 10), even if the former were more likely to have high budding 134. Multivariate analysis showed that high budding was an independent prognostic marker in pT3N0M0 patients, with 5-year cancer-specific survival significantly less comparing high vs low budding groups (63% vs 91%, respectively).

**Lymphocytic Infiltration**

Host immune response to tumour, in terms of a variable amount of peritumoral lymphoid aggregates, also known as Crohn’s-like reaction, or tumor-infiltrating lymphocytes, has been examined as a potential prognostic factor 3 73 135. The most widely applied classification for evaluation of peritumoral lymphoid aggregates recognizes three grades 136: i) no peritumoral lymphoid...
aggregates; ii) mild peritumoral lymphoid aggregates, consisting of occasional aggregates and scattered lymphocytes; iii) marked peritumoral lymphoid aggregates (i.e. numerous aggregates, with or without germinal center formation, and a prominent band of peritumoral lymphocytes). The presence of a marked Crohn-like lymphoid reaction has been reported to be associated with a reduced incidence of lymph node metastases and improved survival. Interestingly, the presence of more than 2 tumor infiltrating lymphocytes per-high power field, as well as a marked peritumoral Crohn-like lymphoid reaction, have been shown to be independent predictors useful in identification of microsatellite unstable (MSI-H) colorectal cancers. Recently, it has been proposed that lymphoid reaction be distinguished into four histological types, comprising Crohn’s-like reaction, peritumoral reaction, intratumoral periglandular reaction, and tumor-infiltrating lymphocytes. This morphological classification was shown to be prognostically relevant because an increasing overall lymphocytic reaction was associated with significant improvement in colorectal cancer-specific and overall survival rates.

**Histologic regression grade after preoperative chemoradiotherapy**

Preoperative chemoradiotherapy has been shown to reduce the risk of local recurrence, thereby improving overall survival in patients with locally advanced rectal cancer. It is widely known that chemoradiotherapy may cause complete tumor disappearance or no evidence of tumor regression. A method to assess tumor response is obtained by grading histological changes in the surgical specimen. Several methods have been proposed, including a 5-tiered score, for tumor regression grading (TRG): i) grade 0, no regression; ii) grade 1 (minor regression) in which tumor is predominant, with treatment-induced fibrosis present in 25% or less of tumor mass; iii) grade 2 (moderate regression) in which tumor is predominant, with treatment-induced fibrosis present in 26% to 50% of tumor mass; iv) grade 3 (good regression) in which fibrosis is predominant, with more than 50% tumor regression; and v) grade 4 (total regression) in which only fibrosis is present, with no viable tumor cells. Subsequently, using the above mentioned 5-tiered score, a study performed in a large series of patients proposed a simplified grading system that stratifies patients into 3 groups: i) complete regression (TRG4); intermediate regression (TRG 2+3); poor regression (TRG 0+1). It was demonstrated that a higher grade of tumor regression was associated with better survival, with 5-year disease-free survival rates, after chemoradiotherapy followed by radical surgical resection, of 86% for complete regression, 75% for intermediate regression, and 63% for poor regression. The above mentioned 3-tiered score (complete, intermediate and poor regression) is the current gold standard for quantification of tumor regression.

In daily practice, it is recommended that at least 4-5 blocks are taken from the tumor mass. If tumor is not grossly evident, any suspicious scarring area should be entirely blocked. If histological examination fails to reveal tumor cells, at least three levels would be cut through each block. The patient can be reported to have complete tumor regression only after meticulous histological examination fails to identify any residual neoplastic focus. In this regard, it should be remembered that chemoradiotherapy may induce the formation of “mucin lakes” in fibrotic areas within the rectal wall. It is recommended to perform several sections to exclude the presence of isolated neoplastic cells within these mucin lakes. Accordingly, use of the pathologic TNM system is strongly recommended (ypTNM) since there is evidence that both the ypT and ypN categories are the most important independent factors.
Fig. 13. A single neoplastic cell in a mucin lake with degenerative changes induced by preoperative radiochemotherapy.

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RECTAL CARCINOMA

Patient Name……………………………………………………….          Date of birth………………………….……    Age…….     Sex………..

Histologic record number………………………………………

GROSS DESCRIPTION

Tumor site in rectal wall: ❑ anterior ❑ posterior

Macrosopic configuration of the tumor:
❑ protuberant ❑ ulcerated
❑ annular stenosing ❑ limitis plastica type

Tumor is
❑ above ❑ at ❑ below the peritoneal reflection

Tumor distance from the dentate line……… cm

Maximum tumor diameter: …….. cm.

Distance of tumor to distal margin: …… cm

Tumor perforation (pT4): ❑ no ❑ yes

Macroscopic assessment of the total mesorectal excision:
❑ complete ❑ nearly complete ❑ incomplete

HISTOLOGY

Tumor type:
❑ adenocarcinoma N.O.S.
❑ mucinous
❑ signet ring cell
❑ squamous cell carcinoma
❑ adenosquamous carcinoma
❑ medullary carcinoma
❑ small cell undifferentiated carcinoma
❑ undifferentiated carcinoma
❑ Other……

Histologic grade: ❑ G1 ❑ G2 (low grade)
❑ G3 ❑ G4 (high grade)

Associated adenoma(s): ❑ no ❑ yes
specify type……………….

Local invasion:
❑ submucosa (pT1)
❑ muscularis propria (pT2)
❑ beyond muscularis propria (pT3)
❑ tumor cells have breached the peritoneal surface (pT4a) or invaded adjacent organs (pT4b)

Circumferential resection margin (CRM) involvement:
❑ Negative margin: distance tumor to CRM …mm
❑ Positive margin : tumor at margin

Type of CRM involvement
❑ direct tumor spread
❑ tumor deposits
❑ perineural tumor spread
❑ vascular invasion ( ❑ lymphatic ❑ venous )
❑ lymph node metastases

Local peritoneal involvement (LPI):
❑ LPI-1: absent
❑ LPI-2: tumor close but not at peritoneal surface
❑ LPI-3: peritoneal surface unequivocally infiltrated
❑ LPI-4: tumor cells lying free in the peritoneal cavity

Distance of invasion beyond muscularis propria:……….. mm

Distal margin involvement: ❑ no ❑ yes

Proximal margin involvement: ❑ no ❑ yes

Tumor budding: ❑ no ❑ yes ( ❑ low ❑ high)

Extramural venous invasion: ❑ no ❑ yes

Total number of lymph nodes examined:…….

Number of metastatic lymph nodes:…….
❑ PN0: no lymph node metastasis
❑ PN1a: 1 lymph node metastasis
❑ PN1b: 2-3 lymph nodes metastasis
❑ PN1c: tumor deposit(s)
❑ PN2a: 4-6 lymph nodes metastasis
❑ PN2b: 7+ lymph nodes metastasis

❑ pT ❑ N ❑ M

Lymphocytic infiltration :
❑ no ❑ yes
❑ Crohn-like ❑ peritumoral ❑ intratumoral

Tumor regression grade
❑ complete (TRG 4)
❑ incomplete (TRG 2+3)
❑ little/absent (TRG 0+1)
Lipoma with osteocartilaginous metaplasia: case report and literature review

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Key words
Lipoma • Osteocartilaginous metaplasia • Case report

Summary
Osteocartilaginous metaplasia in lipomas is rare and mainly encountered in large-sized, long-standing lipomas. This entity can be found at almost any site of the body, particularly in the soft tissues of the skeletal system, breast, pharynx, and nasopharynx. We describe a case of lipoma with osteochondroid metaplasia in a 65-year-old woman with an indolent lesion, and discuss differential diagnoses.

Introduction
Lipomas are the most common benign mesenchymal tumours, and are frequently observed in routine practice of the pathologist. Their variants, angiolipoma, myelolipoma, angiomylipoma, myolipoma, spindle cell lipoma/pleomorphic lipoma and chondroid lipoma are less common. Rarely, especially in the context of lipomas of large size and long-standing duration, areas of bone metaplasia and/or cartilage that characterize osteolipomas and chondrolipomas, are observed. Rare cases of synovial metaplasia have been reported in the literature. For some authors, these variants are “benign mesenchymomas”.

Case report
A 65-year-old Caucasian woman presented to the surgical department of Catania Hospital for the presence of an indolent tumour about 7 cm in largest size, located in the subcutaneous tissue of the right thigh. The patient reported the presence of this lesion for at least 5 years, with a slow and gradual growth. Past medical history was unremarkable, and there was no history of trauma at the site of the lesion. At macroscopic examination, the encapsulated tumour, about 7 cm in largest size, was soft and yellowish and the cut surface showed the presence of translucent whitish nodular areas of hard-elastic consistency, 4 cm in maximum diameter (Fig. 1). The surgical specimen was fixed in 10% formalin and embedded in paraffin. Sections (4-5 μm) were stained with haematoxylin and eosin. Histologically, the lesion was composed of mature adipocytes of varying size. At the cut surface, the areas of hard-elastic consistency corresponded to chondroid metaplasia and focal osteoid metaplasia, without cytological atypia (Figs. 2, 3). Neither necrosis nor haemorrhagic areas were observed. The patient also had a concomitant adrenal pseudocyst with haemorrhagic areas, and microcalcifications in the wall.

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Discussion

Lipomas are frequently observed in surgical pathology. Their variants, although less common, do not pose problems to the pathologist in differential diagnosis. Rarely, bone, cartilaginous and synovial metaplasia can be detected in lipomas of large size and long-standing duration. Many cases of lipoma with osseous/cartilaginous metaplasia have been reported in the literature. They are more commonly referred as osteolipomas and chondrolipomas. Only one case of lipoma with synovial metaplasia is described in the literature. Osteolipomas and chondrolipomas may arise at any anatomical location, but are more frequent in skeletal soft tissue. In the literature, however, cases have been reported in the breast, oropharynx, nasopharynx, eyelid, intraspinal, mediastinum and hypothalamus. A case of congenital osteolipoma of the scalp has also been described. The pathogenetic mechanisms of osteocartilaginous metaplasia in a lipoma are still known. It probably occurs in myxoid areas following to traumatic stress, trophic disorders, or contact with the periosteum. A possible pathogenetic role of certain growth factors such as TGF-beta, LTBP-1 (latent TGF-beta binding protein-1) and BMP (bone morphogenesis protein) has also been suggested. The detection of osteocartilaginous metaplasia in a lipoma is a problem to the pathologist in differential diagnosis with other benign and malignant soft tissue tumours such as chondroma, chondroid lipoma, undifferentiated liposarcoma and chondrosarcoma. In our case, the absence of cytological atypia in areas of osteocartilaginous metaplasia excluded a malignant tumour. A chondroma is characterized by the presence of areas of hyalinized cartilage with multinucleated giant cells, which are not observed in our case. The tumour was also devoid of the typical lobular pattern of chondroid lipoma, where nests of lipoblastic-like cells are immersed in a myxoid/hyalinized stroma. In conclusion, lipomas may show areas of osteocartilaginous metaplasia without clinical prognostic significance. The recognition of these variants is important for correct diagnostic classification of the lesion and the subsequent therapeutic approach.

References

Hemangiopericytoma-solitary fibrous tumour of soft tissue: description of a case showing atypical histological features

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Key words
Hemangiopericytoma • Solitary Fibrous Tumour • Immunohistochemistry • Fish • PCR

Summary
Extrathoracic solitary fibrous tumours have been reported in almost all anatomic sites, but reports of tumours in the extremities or in intramuscular locations, as well as of tumours with atypical histological features and malignant behaviour, are rare.

Herein the authors describe a case of hemangiopericytoma-solitary fibrous tumour that arose in the gluteal region of a 47-year-old woman. The tumour showed atypical histological features, such as high cellularity, increased mitotic activity and focal expression of cytokeratins.

Introduction
Solitary fibrous tumour, formerly considered to be located exclusively in the thoracic cavity, has more recently been increasingly reported in numerous extrapulmonary sites.

Considering that hemangiopericytoma and solitary fibrous tumour share similar histological features, the term hemangiopericytoma-solitary fibrous tumour has been recently adopted and endorsed by the World Health Organization. Such tumours are extremely variable in their histological appearance, depending on the proportion of cells and fibrous stroma. The cellular end of the spectrum corresponds to classic hemangiopericytoma, and the hyalinized end to classic solitary fibrous tumour. Many cases show hybrid features.

Herein we describe the case of a solitary fibrous tumour that arose in the subcutaneous tissue of the gluteal region in a 47-year-old woman and discuss its clinical and pathological features.

Case report
A nodule, 4 cm in diameter, superficially located in the subcutaneous tissue of the gluteal region, in a 47-year-old woman, was excised. The lesion appeared grossly well circumscribed, with a homogenous firm cut-surface. Samples were fixed in formalin, paraffin-embedded and 5 micron sections were obtained for haematoxylin and eosin (HE) and immunocytochemical stainings. Antibodies directed against the following antigens were used: CD34, bcl2, smooth muscle actin, desmin, S100 protein and cytokeratins (MoAbs AE1/AE3).

Microscopically, the tumour appeared to be a mesenchymal, highly cellular neoplasm (Fig. 1) made up of tightly packed, round to fusiform cells with indistinct cytoplasmic borders and mild nuclear atypia, arranged around a rich ramifying vascular network. The vessels showed a large variation in calibre and had a typical sta...
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Moreover, large vessels had a thick coat of hyalinized collagen extending in the interstitium. The most striking histological feature was the consistently high cellular appearance of the neoplasm. Mitotic activity was found to be of 6 mitoses/10 HPF (Fig. 2). No necrosis or haemorrhage were present. The neoplasm showed intense and diffuse positivity for CD34 (Fig. 3) and bcl2. Reactions for desmin, smooth muscle actin and S100 protein were negative in neoplastic cells, but a mild and focal positivity was found for cytokeratins (Fig. 4). Based on histological and immunohistochemical features, a diagnosis of hemangiopericytoma/solitary fibrous tumour with atypical features was made. The case was sent in consultation to an experienced soft tissue tumour pathologist. Due to the positivity for cytokeratins (although focal and mild), the second pathologist proceeded with molecular diagnostic testing to exclude a synovial sarcoma. PCR-RT and FISH analysis excluded the presence of the t(X;18) (p11;q11) translocation. Four months after initial diagnosis, the patient has shown no evidence of recurrent disease.

Discussion

Solitary fibrous tumour, since the original description in 1931 that reported it as arising from the pleura, has been described in a wide range of anatomic sites, including soft tissues. The WHO classification adopted the term hemangiopericytoma/solitary fibrous tumour to indicate a neoplasm that can show histologically different patterns. At one hand, there are neoplasms with features of classic solitary fibrous tumour, consisting of bland spindle cells in alternating hypercellular and hypocellular areas with hyalinized or keloid-like intercellular collagen bundles and prominent branching vasculature with staghorn-like vessels. At the other end of the spectrum, there are neoplasms with a diffuse hemangiopericytomatous-pattern, characterized by a richly vascular network of large and small vessels often with marked perivascular hyalinization; in between the vascular network, the cells of hemangiopericytoma range from round to ovoid. Because of this histologic variability, solitary fibrous tumours occurring at unusual sites can be difficult to diagnose.

In cases with the classic solitary fibrous tumour pattern, diagnosis is usually straightforward, being easily suspected on HE-stained slides and confirmed by the expression of CD34 (observed in 80-90% of solitary fibrous tumours) and bcl2 (observed in 30% of cases). Desmin, cytokeratins and S100 protein are not usually expressed in solitary fibrous tumours. The high sensitivity of CD34 for solitary fibrous tumour has led to more accurate and consistent diagnosis of this entity. Nevertheless, especially when tumours do not show the classic histological pattern, diagnosis is not necessarily straightforward and can require additional techniques. In the present case, the neoplasm had characteristic histological features, being very cellular and showing a diffuse hemangiopericytomatous pattern of growth. The tumour exhibited diffuse positivity for CD34 and bcl2, in agreement with the diagnosis of solitary fibrous tumour/hemangiopericytoma, but showed also focal and mild positivity for cytokeratins. The possibility of a positive reaction for cytokeratins has been reported in the literature in a few cases of solitary fibrous tumour, especially in hypercellular or sarcomatous areas.

The most difficult differential diagnosis, especially when solitary fibrous tumour is not classic and is highly hypercellular, is with monophasic synovial sarcoma that can
exhibit a distinctive hemangiopericytoma-like pattern. Synovial sarcomas are usually positive for cytokeratins, EMA and bcl2 and can, although very rarely, express CD34. In our case, in order to rule out a monophasic synovial sarcoma, additional molecular studies using FISH and RT-PCR for the presence of the t(X;18) translocation, involving the rearrangement of SYT and SSX genes, were performed. This translocation is specific for synovial sarcoma, but was not detected in our case. The majority of hemangiopericytoma/solitary fibrous tumours thoracic and extrathoracic sites are histologically benign and follow a benign clinical course; however, solitary in fibrous tumours from any anatomic site can recur and metastatize after surgical resection. Vallat-Decouvelaere et al. reported their experience from a large consultation service and indicated that approximately 10% of extrathoracic solitary fibrous tumours have atypical features or a history of local recurrence. Atypical features included increased cellularity, nuclear atypia, > 4 mitoses/10HPF and necrosis. The behaviour of solitary fibrous tumour cannot always be accurately predicted from histological findings, since isolated cases with no atypical histological features have been reported to develop local recurrence or distant metastases. Extrathoracic and intrathoracic solitary fibrous tumours appear to have a similar clinical behaviour and can recur or metastasize after complete resection, even after more than 5 years, either in the presence or absence of atypical histological features. Complete surgical excision and long-term follow-up are advisable for all patients, and it is probably unwise to regard any such lesion as definitely benign.

References

The use of placental S100 (S100P), GATA3 and Napsin A in the differential diagnosis of primary adenocarcinoma of the bladder and bladder metastasis from adenocarcinoma of the lung

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Key words
Adenocarcinoma • Bladder • Lung • GATA3 • Placental S100 • Napsin A

Summary
Primary bladder adenocarcinoma accounts for 0.5-2% of all malignant bladder tumours. Literature data indicate the bladder as the second most common site of metastatic genitourinary tumours, with the kidney as the most frequent location. Secondary tumours of the bladder account for about 2.3% of all bladder malignancies encountered in surgical specimens. Herein, we describe an adenocarcinoma deeply infiltrating the bladder wall, with no morphologic features of transitional cell carcinoma, in a patient with a previous diagnosis of primary lung adenocarcinoma, mixed subtype.

In this case, the use of a limited immunohistochemical panel including napsin A, a recently described highly sensitive marker for lung adenocarcinoma, GATA3 and S100P, two novel markers of urothelial differentiation, was of crucial importance in differentiating between lung adenocarcinoma metastatic to the bladder and primary bladder adenocarcinoma.

Case report
A 63-year-old woman, cigarette smoker, presented with clubbing and joint pain. A chest X-ray and CT scan showed a 5 cm mass located in the right lower lobe of the lung. The CT scan of the abdomen was negative. Lobectomy with mediastinal lymphadenectomy were performed. Histological examination revealed a moderately to poorly differentiated adenocarcinoma, mixed subtype, with acinar, solid and papillary patterns. Lymph nodes were negative. The patient did not undergo adjuvant therapy.

After 10 months, a follow-up pelvic CT scan showed a solid lesion, measuring 3 cm in diameter, in the left side of the bladder wall. The lesion was endoscopically resected, and histologic examination showed an adenocarcinoma deeply infiltrating the bladder wall, with no morphologic features resembling transitional cell carcinoma.

Haematoxylin and eosin stained sections of both lung and bladder tumours were reviewed and immunohistochemical staining was performed on representative sections. The primary antibodies used were: CK7 (clone OV-TL12/30, Ventana Medical System; Ready-to-use; retrieval CC1), CK20 (clone Ks 20.8, Ventana Medical System; Ready-to-use; retrieval CC1), CDX-2 (clone EPR2764Y, Ventana Medical System; Ready-to-use; retrieval CC1), TTF-1 (clone 8G7G3/1, Ventana Medical System; Ready-to-use; retrieval CC1), (all from Ventana, CA, Usa), Napsin A (clone TMU-Ad02, American Research Products – ARP – Belmont, MA 1:500 retrieval pH6), GATA3 (clone L50-823, BD-Biosciences, San Jose, CA, 1:150, retrieval pH 8) and placental S100P (clone 16, BD-Biosciences, 1:1000, retrieval pH 6).

Histologic features were not useful in differentiating primary or secondary bladder tumour. Immunohistochemical studies showed different profiles in the two tumours: in the lung carcinoma diffuse CK7 staining was seen, together with focal/weak TTF-1 immunoreactivity and strong/diffuse napsin-A immunoreactivity (Fig. 1). CK20, CDX-2, S100P and GATA-3 were completely negative in neoplastic cells. On the other hand, the bladder adenocarcinoma showed positive immunoreactivity.
for CK7, S100P (Fig. 2), and GATA 3 (Fig. 3), whereas CK20, CDX-2, TTF-1 and napsin A were negative. The immunohistochemical results were crucial for establishing the final diagnosis of primary bladder adenocarcinoma. In particular, the use of GATA3, S100P and Napsin A was particularly informative. On the basis of this diagnosis, the patient underwent radical cystectomy, hysterectomy, bilateral salpingo-ovariectomy and lymphadenectomy. Histologic examination of the surgical specimens confirmed the diagnosis of bladder adenocarcinoma, not otherwise specified (NOS), with low grade of differentiation. The tumour infiltrated the bladder wall with a microscopic infiltration of the perivesical fat; lymph nodes, uterus and ovaries were negative.

**Discussion**

Primary bladder adenocarcinoma accounts for 0.5-2% of all malignant bladder tumours. There are different subtypes of bladder adenocarcinoma, including the enteric type, signet-ring cell type, colloid type, clear cell type, and not otherwise specified (NOS) adenocarcinoma.

The immunohistochemical markers commonly used to better define these subtypes of bladder adenocarcinoma are not specific and quite variable in their results, and thus the profiles obtained may also resemble those characterising intestinal or lung adenocarcinomas.

Data from the literature indicate the bladder as the second most common site of metastatic genitourinary tumours, with the kidney being the most frequent location. Secondary tumours of the bladder account for about 2.3% of all bladder malignancies encountered in surgical specimens. The most common primary sites are the colon (21% of secondary neoplasms), prostate (19%), rectum (12%) and cervix (11%). These tumours are known to reach the bladder mainly by direct spread. Less frequently, tumours from distant sites may metastasize to the bladder, namely the stomach (4.3% of all secondary neoplasms), skin (3.9%), breast (2.5%) and lung (2.8%).

Bladder secondary tumours are almost always solitary, and the majority of cases have been reported to be adenocarcinomas. Moreover, secondary adenocarcinomas of the bladder seem to be slightly more frequent than primary lesions.

The distinction between primary and secondary adenocarcinoma of the bladder is a common diagnostic problem in this site and implies relevant differences in treatment modalities. Proper clinical history is one of the most important factors in suggesting a correct diagnosis. Nonetheless, a second primary tumour may not be confidently excluded, and the difficulties are even more evident when analysing small biopsy specimens. Primary and secondary adenocarcinomas of the bladder may closely resemble each other and show no morphological differences.

Immunohistochemistry has traditionally been thought to be of limited utility in differential diagnosis due to
the lack of highly sensitive and/or specific markers for bladder epithelial cells. In recent years, new antibodies with distinct reactivity for pulmonary and bladder cells (Napsin-A, GATA3, S100P) have been proposed as useful markers and have become available in routine laboratory practice. Napsin A is a functional aspartic proteinase restricted to type 2 pneumocytes and to the epithelium of the proximal and convoluted tubules of the kidney. Napsin A has been found to be positive in up to 89% of primary lung adenocarcinomas, although its expression seems to decrease with increasing tumour grade. Systematic studies on the expression of napsin A have found this marker to be more sensitive than TTF-1 in the positive diagnosis of primary lung adenocarcinoma.

S100P is a member of the S100 family of proteins, initially identified in the placenta. S100P is expressed in 78% of bladder urothelial carcinomas. GATA3 is also a potential new marker of urothelial differentiation. The sensitivity of GATA3 for urothelial carcinomas, 66.9%, is lower than that of S100P, but its specificity appears to be rather high.

In the present case, the use of a limited immunohistochemical panel including napsin A, a more sensitive marker for lung adenocarcinoma, GATA3 and S100P, two novel markers of urothelial differentiation, was of crucial importance in differentiating between lung adenocarcinoma metastatic to the bladder and primary bladder adenocarcinoma.

References

CASE REPORT

Cystic struma ovarii: a report of three cases

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Key words

Ovary • Struma • Cystic

Summary

Three cases of cystic struma ovarii in women aged 16, 20 and 40 are described. All patients had an asymptomatic ovarian mass at ultrasound scan. The tumours, all of which were unilateral and confined to the ovary, ranged from 7 to 10 cm in the greatest dimension. Two lesions were unilocular, the third multilocular, and all were filled with green fluid. Microscopic examination showed cysts with fibrous wall lined by non-specific-appearing epithelial cells. In the wall of the cysts, there was a small number of thyroid follicles. In one case, an association with a cystic mature teratoma was seen. The paucity of thyroid follicles and the non-specific appearance of the epithelial cells required a careful sampling and immunohistochemical staining for thyroglobulin to establish an exact diagnosis. The postoperative period was uneventful and thyroid function remained normal. In conclusion, cystic struma is probably often underdiagnosed and should be considered when evaluating cystic ovarian tumours whose features are not obviously those of another tumour type. A careful search for thyroid follicles should be undertaken. In problematic cases immunohistochemical staining for thyroglobulin may be required.

Introduction

Struma ovarii is the most common monodermal mature teratoma of the ovary, representing about the 2.7% of all teratomas 1. The tumour is generally benign, although malignant transformation has been reported 2,3. The literature regarding the pathology of struma ovarii has focused principally on the problem of formulating criteria for malignancy 4. In contrast, unusual microscopic features and extreme morphological variability 5, which can cause diverse problem in differential diagnosis, have received relatively little attention. The criteria for diagnosis is the presence of thyroid tissue, typically in the form of follicles containing colloid. In some cases, on low-power microscopic examination, the appearance can be a diffuse pattern of growth, with rare microfollicles, or a trabecular or pseudotubular arrangement. As many other ovarian tumours, struma may be entirely cystic, unilocular or multilocular, with only a few small follicles in the fibrous septa. In such cases, the cyst wall is generally lined by flat or cuboidal non-specific epithelium. Preoperative differential diagnosis between different ovarian cystic neoplasms is generally difficult; in cases of completely cystic struma, even histologic diagnosis can be problematic. The clinical and pathological features of three cases of cystic struma ovarii are described.

Clinical features

Between Nov 1, 2006 and Feb 1, 2009 three patients (age 16, 20 and 40) were referred to the Dept. of Gynaecology and Obstetrics due to the presence of an ovarian mass visible by pelvic ultrasonographic examination. Physical examination was unremarkable. In all three patients, the ovarian tumour was an incidental finding; two women were asymptomatic, while the other complained of menometrorrhagia. All lesions were unilateral and organ-confined. Serum Ca125 levels were normal. In one case, there was family history of thyroid disease (papillary carcinoma). Two patients underwent laparoscopic dissection of the cyst, the third total abdominal hysterectomy, because of the presence of uterine leiomyoma that caused menometrorrhagia, with concomitant resection of the ovarian lesion. The postoperative period was uneventful and thyroid function remained normal.

Gross pathology

The tumour sizes were 7, 8 and 10 cm. The external surface was intact and smooth. Sectioning showed uniformly cystic neoplasms, two unilocular and one multilocular, containing brown-greenish gelatinous fluid.
The fibrous wall had variable thickness, with rare small cavities (diameter 2-4 mm) in this context.

**Microscopic pathology**

On low-power microscopic examination, the cyst walls and septa were composed of loose fibrous tissue, focally hyalinized, with scattered inflammatory cells. The lumens contained eosinophilic material, occasionally admixed with pigment-laden histiocytes. Within the septa, small thyroid follicles were identified (Fig. 1) in all cases, but only on few slides and in small areas. Some follicles contained colloid, but some were empty. Cysts and follicles were lined by non-specific flat-cuboidal epithelium, with scanty cytoplasm and round nuclei without atypia (Fig. 2). Mitoses were absent. Epithelial cells were strongly positive when stained for thyroglobulin (Fig. 3). An adjacent dermoid cyst was recognized on microscopic examination in one case.

**Discussion**

About 5-20% of ovarian teratomas may contain thyroid tissue, but the term “struma ovarii” is only applied to teratomas composed either predominantly or exclusively of such tissue. It is a rare benign neoplasia, but is the most common monodermal teratoma, accounting for 2.7% of all ovarian teratomas. Cases of malignant struma ovarii have been previously described and most of the available literature has focused on the study of morphologic criteria of malignancy. Another feature of these tumours is the possible association with abnormal thyroid function. The morphologic variations that may lead to misinterpretation have not been widely considered. Three cases of entirely cystic struma whose diagnosis was difficult for the extreme paucity of recognizable thyroid tissue are described herein.

Clinical features are non-specific: the lesions were monolateral, limited to the ovary, with a diameter less than 10 cm, like most monodermal teratomas. The ultrasonographic pattern was similar to that of other cystic ovarian neoplasms. In agreement with other observations, there were no specific presenting symptoms, and the tumours were discovered during routine ultrasound studies. On gross inspection, there are no macroscopic clues leading to correct diagnosis other than the presence of a green-brown colour of the content. Szyfelbein et al. indicates that such a colour should always suggest the diagnosis of struma, because it is only rarely observed in other cystic neoplasms. In two cases, microscopic diagnosis was particularly difficult because of the extreme paucity of thyroid tissue. The epithelial lining of the cystic wall was non-specific. Rare small follicles were present in limited areas, where the wall was thicker. The absence of cilia or intracellular mucin was a clue that the cyst was not serous or mucinous, but immunohistochemical staining for thyroglobulin was necessary to make a correct diagnosis. In the other case, the diagnosis was easier due to the microscopic finding of an associated dermoid cyst.
Although it has been known for many years that struma ovarii may have a prominent cystic component, pure cystic tumours have been reported infrequently and without indication that the interpretation of these tumours caused difficulty. One microscopic diagnostic clue is the presence of unequivocal thyroid tissue in the wall or septa of the cyst. Thyroid follicles may be very small, rare and confined to a limited area. In these cases, a diffuse sampling of the surgical specimen is necessary, particularly where the wall of the cyst is thicker. A careful microscopic search of the thyroid tissue is essential, but a confirmatory immunohistochemical staining for thyroglobulin is helpful and sometimes necessary. In conclusion, cystic struma ovarii is probably frequently underdiagnosed. Surgical pathologists, if not in a specialist hospital, should be aware of this diagnosis, also because, in recent years, minimally invasive laparoscopic surgical techniques have improved the treatment of adnexal masses. When a cystic ovarian neoplasm does not have morphological features typical of an epithelial tumour of the ovary, a diagnosis of cystic struma should be taken in consideration. The suspicion should rise if a green or brown colour of cyst content, or an associated dermoid cyst, is noted. A wider sampling of the surgical specimen is advisable, particularly where the cystic wall is thicker. If thyroid follicles are rare, the immunostaining with thyroglobulin is useful. Additionally, flattened epithelium of the cyst stains positive for thyroglobulin, so a diagnosis is still possible when no follicles are recognizable.

References

The new “Atlas of Tumor Pathology” series published by AFIP is written by two well-known authors that have as much clinical and academic experience in the field of the breast pathology as anyone. The book, printed hard cover, is composed of 18 chapters, appendix, and contents sections. This 418-page book is traditionally conceived as an atlas, and since surgical pathology is predominantly a morphologic profession, it’s nice to have access to a large number of high-quality illustrations, all full-colored and easily referenced. Among the enriching changes in this edition is the inclusion of an online electronic version with purchase of the hard copy, that is easy to use and with obvious advantages in copying segments or extracting pictures and references in printable and transferable formats. The text describes the entire range of breast pathologies, and there is little that this book does not cover. After the first two chapters describing normal anatomy and benign lesions, lobular and ductal proliferative lesions and in situ carcinomas are illustrated according to Tavassoli’s approach and current LIN & DIN terminology. A number of tables summarize the basic features of this approach compared to conventional and WHO classifications. In the chapter on papillary lesions of the breast, among papillomas and papillary carcinomas, invasive micropapillary carcinoma is curiously included, which is a true well-established “pseudopapillary” neoplasm with characteristic morphologic, molecular and prognostic features. It might have been preferable to describe this entity in the section on “uncommon variants of carcinoma” to avoid some confusion among neophytes or even rusty general pathologists. A very useful chapter deals with “staging of breast carcinoma and prognostic and predictive indicators” in which the authors incorporate the application of the most recent knowledge on the subject, including the latest scientific achievements, from sentinel lymph node and micrometastases, immunohistochemical and molecular techniques to tissue and DNA microarrays. Breast carcinomas are divided and discussed in three separate chapters: 1) major variants, including invasive ductal NOS, and invasive lobular carcinomas; 2) carcinomas of low-grade malignancy; and 3) uncommon variants of carcinoma. Each tumor type is described by definition, clinical features, pathologic findings, differential diagnosis, histogenesis and information about treatment and prognosis. For most, when appropriate, fine needle aspiration cytology (FNAC) details are also provided. In the last group, among very rare carcinomas such as metaplastic, apocrine, lipid-rich, sebaceous, secretory, glycogen-rich, melanotic, etc., all identifiable through specific microscopic features, “basal-like breast carcinomas” were unexpectedly included, which are currently considered a highly phenotypically and biologically heterogeneous group, best characterized by gene expression profiles. The chapter on “myoepithelial lesions” is clearly treated and superbly illustrated, throwing light on terminology issues and giving precious information on diagnostic algorithm. Finally, preoperative diagnostic procedures such as intraoperative frozen sections, fine needle aspiration cytology (FNAC) and needle core biopsy (NCB) are mentioned in the appendix. Macro (large) section technique is also explained, and a synoptic reporting proposal of Association of Directors of Anatomic and Surgical Pathology (ADASP) is also mentioned. In conclusion, this book is everything we have come to expect from the Armed Forces Institute of Pathology fascicle series and may truly be a classic, marking both a new pinnacle of the authors’ careers and the field of breast pathology itself.

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<tr>
<td>09.00 – 10.30</td>
<td>SIAPEC-IAP incontra la SICI</td>
<td>Sessione AITIC 1</td>
<td>Comunicazioni: Premio Rotary Bologna</td>
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<tr>
<td>10.30 – 11.00</td>
<td>Patologia ginecologica nella sindrome di Lynch</td>
<td>La SIAPEC-IAP incontra l’Adriatic Society of Pathology 25th year</td>
<td>Comunicazioni: Premio Susan G. Komen</td>
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<tr>
<td>13.00 – 14.30</td>
<td>Patologia da trapiant</td>
<td>La diagnostica molecolare dei tumori solidi oggi. Un’approccio pratico per patologia d’organo</td>
<td>Comunicazioni: Premio Pathologica</td>
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<tr>
<td>14.30 – 16.30</td>
<td>Patologia della tiroide. Lesioni tiroidee non convenzionali e problemi diagnostici emergenti</td>
<td>Patologia ginecologica nella sindrome di Lynch</td>
<td>La SIAPEC-IAP incontra l’Adriatic Society of Pathology 25th year</td>
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<tr>
<td>16.30 – 16.45</td>
<td>Caffé</td>
<td>Slide Seminar Mammella</td>
<td>Slide Seminar Tessuti molli e osso</td>
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<td>16.45 – 18.30</td>
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<tr>
<td>Giovedì 23 settembre 2010 – Palazzo della Cultura e dei Congressi</td>
<td>Auditorium Europa</td>
<td>Sala Italia</td>
<td>Sala Azzurra</td>
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<td>09.00 – 10.30</td>
<td>Virchows Archiv Symposium: Patologia enteropancreatica</td>
<td>La SIAPEC-IAP incontra l’AIOM</td>
<td>Corso di citologia</td>
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<td>10.30 – 11.00</td>
<td><strong>Caffè</strong></td>
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<td>11.00 – 13.00</td>
<td>Neoplasie del colon</td>
<td>Patologia cardiaca</td>
<td>Citologia 1</td>
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<td>13.00 – 14.30</td>
<td><strong>Pranzo</strong></td>
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<td>14.30 – 16.30</td>
<td>Corso Patologia polmonare</td>
<td>Malattie infiammatorie gastrointestinali</td>
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<td>16.45 – 18.30</td>
<td>Slide Seminar Neoplasie polmonari</td>
<td>Le malattie da malassorbimento intestinale</td>
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## Tavole Sinottiche

### Venerdì 24 settembre 2010 – Palazzo della Cultura e dei Congressi

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<th>Sala Bianca</th>
<th>Sala Rossa</th>
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<tbody>
<tr>
<td>09.00 – 10.30</td>
<td>Simposio</td>
<td>L’emergenza</td>
<td>La SIAPEC–IAP</td>
<td>Comunicazioni</td>
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<td>di emo-linfo patologia: l’esperienza WHO</td>
<td>cancro in Africa: la diagnosi anatomopatologica in un approccio multidisciplinare</td>
<td>incontra l’AIRTum</td>
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<td>10.30 – 11.00</td>
<td>Procedure e linee guida</td>
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<td>11.00 – 13.00</td>
<td>Patologia neoplastica della vescica e prostata</td>
<td>Slide Seminar Surgical pathology dei linfomi</td>
<td>Uomini e donne in patologia, la forza delle radici</td>
<td>SNOMED-NAP</td>
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<td>Assemblea Societaria</td>
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<td>16.30 – 17.00</td>
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<td>La rete di biobanche di tessuti di archivi in Italia</td>
<td>Cellule staminali in patologia tumorale</td>
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<td>17.00 – 19.00</td>
<td>Governance anatomo-clinica</td>
<td>Patologia del trofoblasto</td>
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<td>21.00</td>
<td>Cena “I migliori Ristoranti di Bologna”</td>
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### Sabato 25 settembre 2010 – Palazzo della Cultura e dei Congressi

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<tr>
<td>08.30 – 10.30</td>
<td>Slide Seminar Istopatologia</td>
<td>I giovani in Europa: la formazione dell’anatomo-patologo</td>
<td>Problematiche di neuropatologia</td>
<td>Comunicazioni</td>
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<td>Slide Seminar Patologia epatica</td>
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<td>11.00 – 12.00</td>
<td>Sessione Plenaria</td>
<td>La struttura del nucleo e suo significato in patologia</td>
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<td>12.00</td>
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<td>G. Bussolati</td>
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<td>Proclamazione del nuovo direttivo e chiusura del congresso</td>
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