Conclusion and Remarks

19

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High Prevalence of Bladder Cancer

Bladder cancer is one of the most common cancers in the world, and it is especially prevalent in males [1]. The lifetime risk worldwide of developing urinary bladder cancer is 1.1% for males and 0.27% for females [2]. Globally, approximately 550,000 new cases were diagnosed in 2018 (approximately 425,000 males and 125,000 females) [2]. The survival rate of bladder cancer patients is also relatively high. In the United States, the 5-year relative survival rate for all bladder cancer patients is 77%. Of the 81,400 new cases of bladder cancer projected to be diagnosed in 2020 in the United States, 17,980 people will die from the disease [3]. The high survival rate is largely because of the diagnosis of non-muscle-invasive bladder cancers (NMIBC) in approximately 70–80% of new patients, including noninvasive papillary tumor (pTa), carcinoma in situ (CIS; pTis), or early invasive tumor (non-muscle-invasive; pT1). These tumors can be managed locally with transurethral resection of bladder tumor (TURBT) and intravesical chemotherapy or Bacillus Calmette-Guérin (BCG) treatment. The 5-year survival rate of pTa and pTis patients is reported to be 96% [3]. Approximately 10–20% of NMIBCs progress to muscle-invasive bladder cancer (MIBC). Characteristically, 50–70% of these cases recur [4, 5]; thus, the volume of bladder cancer surveillance cases is considerable. With increasing levels of treatment development and improved health care, bladder cancer survival rates are expected to increase, leading to a subsequent increase in the prevalence of bladder cancer [1].

The average age for an initial diagnosis of bladder cancer is 65–70 years. Global population growth and aging will increase the number of bladder cancer cases. The United Nations has reported that the world population is expected to increase from an estimated 7.7 billion people worldwide in 2019 to around 8.5 billion people in 2030 and then to 9.7 billion people in 2050 [6]. The number of persons more than 60 years of age is expected to double by 2050 to a projected 2.1 billion people [7]. With continuing population growth and aging, more bladder cancer cases are expected to be diagnosed. Pathologists are expected to see a high volume of bladder cancer cases, and bladder pathology will continue to be a common practice field.

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Diagnostic Challenges and Clinical Management of Bladder Cancer

Cystoscopy with biopsy or TURBT requires the pathological evaluation of muscle invasiveness. T1 tumors invade lamina propria but are not muscle-invasive, and their clinical course and treatment are more like Ta tumors. Ta and T1 tumors are grouped as non-muscle-invasive tumors and are usually treated locally. Treatment of muscle-invasive tumors often involves a radical cystectomy, if operable. During microscopic evaluation, the presence or absence of muscularis propria should be documented. Hyperplastic muscularis mucosa can mimic the thick muscle bundles of the muscularis propria [8, 9], and sometimes a repeat biopsy or further studies with immunostains may be required.

Histological variants account for approximately 25% of bladder cancer cases, which poses a challenge for the practice of bladder pathology. The identification of these histological variants has important diagnostic, prognostic, and therapeutic implications [10]. The recognition of non-muscle-invasive micropapillary urothelial carcinoma warrants an early radical cystectomy in most medical centers because of its aggressive behavior [11]. The presence of sarcomatoid urothelial carcinoma suggests a poor prognosis: one large series study showed that median survival was only 18.4 month following diagnosis [12]. Plasmacytoid feature is an independent prognostic factor for overall survival for plasmacytoid urothelial carcinoma, which is associated with adverse clinicopathological features and worse overall mortality compared to the conventional urothelial carcinoma [13, 14]. Besides urothelial carcinoma variants and other non-urothelial type primary carcinoma, secondary malignancies can occur in the bladder from metastasis or local extension. Recognizing these uncommon entities determines appropriate clinical management.

With the prolonged survival of bladder cancer patients, thanks to early detection and advances in treatment regimens, surveillance biopsy plays a critical role in monitoring patients local resection, intravesical treatment, and chemotherapy or radiation therapy. Pathological challenges include differentiating recurrent tumoral lesions from metaplastic changes that may happen frequently after variable treatments on bladder mucosa and differentiating tumoral lesions from reactive changes such as post-biopsy reparative changes, hemorrhagic cystitis, or radiation cystitis. Stromal changes may mimic mesenchymal sarcoma which can happen de novo or post-radiation. Morphologic diagnosis, therefore, is critically important for patient management, and pathologists must be familiar with all aspects of bladder pathology.

Pathological Diagnosis and Clinical and Radiological Findings of Bladder Cancer

The diagnosis of bladder cancer should never happen in a black box. Microscopic findings should be correlated with clinical pictures. The patient's clinical presentation, urine analysis, cytology, systemic review, and past medical history can all aid in the accurate evaluation of histologic tissue.

Cystoscopy is important and necessary for the diagnosis of bladder cancer. Pertinent gross features of the tumor (location, size, number, and most importantly, flat or papillary appearances) and other mucosal abnormalities can be ascertained during cystoscopy. Therefore, cystoscopic images and reports are extremely helpful for pathologic evaluation.

Imaging studies are not often used as the first modality to evaluate bladder cancer. However, both computerized tomography (CT) and magnetic resonance imaging (MRI) may be used for assessment of local invasion, primarily to detect T3b disease or higher. Recent studies have also shown that MRI combined with diffusion-weighted imaging can differentiate T1 or less tumors from T2 or greater tumors before surgery with a 91% sensitivity and 96% specificity [15]. CT and MRI detection of regional lymph node metastasis has low sensitivity and specificity. Staging for distal metastases can best be done with CT [16, 17]. Imaging studies can also help with the diagnosis of bladder mesenchymal

tumors when bladder mucosal change is nonexistent or minimal. Adjacent organ abnormalities from the bladder (prostate, rectum, uterus, etc.) can also be visualized with CT or MRI and can broaden the differential diagnosis when pathologists are evaluating tissue procured from the bladder when the diagnosis of a secondary tumor is considered.

Molecular Pathology of Bladder Tumors

Despite the prevalence of bladder cancer worldwide, few advances have been made in the clinical management of bladder cancer in recent years, largely due to the poor understanding of its molecular signatures. Bladder cancer is pathologically and molecularly heterogeneous, and molecular profiling studies and whole genomic sequencing have helped to categorize bladder cancer into subtypes that are associated with different prognoses and responses to therapies [18]. These details have been discussed in depth in Chap. 14. These molecular advances have already helped to shift pathology practice forward. With sound molecular techniques, pathologists can now provide more accurate information for tumor prognosis, help to design appropriate treatment regimens, and predict treatment efficacy. With the development of molecular pathology, urologists and urological oncologists have many more options to provide tailored precision medicine for bladder cancer patients with molecularly defined tumor subtypes.

Digital Pathology and the Use of Artificial Intelligence in Bladder Cancers

Because of the rapid development of computer technology and Internet innovations, digital pathology, including the use of digitized whole-slide images for computational analysis aided by artificial intelligence (AI), has advanced greatly in recent years [19]. AI-based approaches for the detection, segmentation, diagnosis, and analysis of digitized images were first compared with conventional microscopy in 2018 in a large-scale multicenter comprehensive study [20] that demonstrated that the diagnostic performance of WSI was comparable to that of traditional microscopy-based approaches. With deep learning approaches, AI-based analyses have a similar level of accuracy to that of expert pathologists [21–23].

Computer engineers and data scientists have focused on the development of new AI-based image analysis approaches in pathology and oncology to improve diagnostic accuracy and to identify novel biomarker for precision medicine. As end users, pathologists need efficient digital slide scanners, cloud-based database, and appropriate AI algorithms to instantly share images with AI-based predictions worldwide. A detailed discussion of these technologies is beyond the scope of this book, but to learn more, readers can refer to other recent publications [19].

With the continuing expansion of computer science and AI, remote online pathology practice with the aid of advanced internet technology is a very promising development for pathologists to embrace in the near future.

Remarks

This book has extensively summarized recently published data about urothelial carcinomas and other bladder lesions. However, due to the rapid evolution of our understanding of bladder cancer and numerous recent publications, there are omissions in this book for newly published papers. This book is a summary of the authors' knowledge, expert understanding of these diseases, and the best angles of approach for diagnosis in bladder pathology. Numerous other professional books, including pathology books, have been published regarding bladder cancer. Our book will serve as an addition to the collective knowledge regarding bladder cancer, particularly in its pathological diagnosis. It is our hope that readers will benefit from our book and that practicing pathologists and pathology trainees will maximize their diagnostic ability aided by the guidance of this and other related books.

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