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Review

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The Current Diagnosis of Superficial Bladder Cancer Must Be Reconsidered

Abstract

The high recurrence and progression rates in superficial bladder cancer are partially related to the deficiencies of the standard conventional diagnostic modalities. Therefore, innovative noninvasive and invasive detection devices have been studied during the last decade. New diagnostic urine markers are under intensive investigation in order to exclude the presence of urothelial cancer, but the value of all these tests is still insufficiently validated in diagnosis and follow-up. With the introduction of 5-aminolevulinic acid fluorescence endoscopy, the efficacy of the detection device has been significantly improved. Flat lesions such as carcinoma in situ can be completely detected besides exophytic tumors. This is of particular importance because the fate of the patient depends to an important extent on these tumor entities. Furthermore, first experimental results using imaging devices like optical coherence tomography and confocal laser scanning microscopy promise new powerful noninvasive tools for 'optical sectioning' of the bladder.

Introduction

Bladder cancer is the sixth most frequent malignant disease in the world. Superficial stages are found in approximately 75–85% of the patients upon first diagnosis; 50–70% of the patients with superficial tumors suffer one or several recurrences after the initial treatment, and in about one third of the patients a progression is observed [1]. The mechanisms for tumor recurrence and/or progression can be summarized as follows: (1) subsequent new tumor occurrence; (2) implantation of tumor cells at the time of transurethral resection (TUR); (3) incomplete tumor resection, and/or (4) overlooking of the concomitant presence of flat urothelial lesions like dysplasias and carcinomas in situ [2]. Therefore, the current diagnosis of superficial bladder cancer requires a thorough review in many respects.

Conventional Diagnosis of Superficial Bladder Cancer

Cytoscopic evaluation of the bladder, routine cytology, and random biopsy are the main diagnostic tools since many decades and can be considered the current 'gold standard'. Although many aspects of the management of superficial bladder cancer are now well established, significant challenges remain which influence the patient outcome. Early detection and treatment of recurrent disease is required to maximize bladder preservation and patient survival. Especially in cases of flat urothelial lesions, conventional endoscopy is not sufficient to reveal areas of carcinoma in situ or dysplasia. However, it is mainly this tumor entity that determines the patient's prognosis. If dysplasia or carcinoma in situ is found in mucosae of normal appear-

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ance, the risks of suffering a muscle-infiltrating recurrence within 4 years are 36 and 83%, respectively [3]. Therefore, early recognition of a carcinoma in situ is essential to offer the patients the most appropriate treatment and the highest cure rate.

Cytological investigation of the urine is a noninvasive and an important adjunct to the diagnosis of bladder cancer. Whereas the sensitivity of cytology is high for carcinomas in situ and high-grade neoplasms, it is rather low for low-grade tumors and dysplasias [4]. Nevertheless, the WHO consensus classification from 1999 [5] classified the moderate dysplasia as high-grade intraurothelial neoplasia like carcinoma in situ. Moreover, the sensitivity calculations only relate to the cases in whom visible tumors were present at the same time. Unfortunately, it is not surprising when Giella et al. [6] found a sensitivity of only 40% for urine cytology in follow-up investigations of bladder cancer patients.

However, in case of positive cytology and normal appearing mucosa, random biopsies are recommended by several authors. In contrast, other investigators believe that random biopsies are an insufficient method for detecting flat lesions [7]. In a retrospective study Kiemeney et al. [8] found no correlation between patient outcomes whether select mucosal biopsies were not performed or if done were normal. However, if dysplasias or carcinomas in situ were found, the patients had a statistically significantly higher risk of tumor progression. Therefore, random biopsies seem to be inadequate, since relevant early-stage and precancerous lesions are often missed [8].

Regardless of the questionable wisdom of obtaining selected mucosal biopsy specimens, there is no doubt that the standard repertoire for the detection of flat lesions requires improvement.

But, however, not only dysplasias and carcinomas in situ are the potential cause of the high rates of recurrence and progression of bladder carcinomas, but also tumors that have been overlooked or left behind in TUR.

The risk of overlooking neoplastic lesions of the bladder using white-light endoscopy is significant. After TUR of superficial bladder cancers, tumor remnants were found in up to 43% of the cases at repeated resection 1–2 weeks later [9, 10]. Even in solitary superficial bladder tumors, residual disease was found in 24% of the patients at a second TUR 5 weeks later. The authors underlined the quality of their first resection by the fact that the second resection revealed infiltrative growth in only 2% of the cases. Therefore, most of these overlooked neoplasms stemmed from positive margins or heterotopic lesions.

Klän et al. [11] reported a fractionated resection of T1 transitional cell cancer. In 28% of the patients positive tumor margins were found, while residual disease from the tumor base was not observed in any case. A routine second resection was carried out 8–14 days later and revealed residual disease in 50% of the patients despite the surgical report of complete resection. 76% of the missed lesions were found to be visible tumors at repeated resection. These authors concluded that the extent of the lesions can easily be misjudged even by experienced surgeons.

New Diagnostic Procedures

In view of the above-mentioned deficiencies, during the last decade efforts have been made to improve the invasive and noninvasive detection of superficial bladder cancers.

Noninvasive Tests

The use of a noninvasive marker test to exclude the presence of urothelial cancer was extensively investigated in recent years. One of the most studied new marker tests for bladder cancer is the bladder tumor antigen (BTA) test. The BTA test is a latex agglutination assay for the qualitative detection of BTA in the urine. The antigen is composed of basement membrane complexes that have been isolated from the urine of bladder cancer patients. Several groups have investigated the BTA test, but nevertheless its place still remains unclear, especially in patients with urinary tract infections [12–14].

Another test used by several investigators is the nuclear matrix protein 22 test. Normal subjects have been shown to have low levels of nuclear matrix protein 22 in their urine as compared with patients with active bladder cancer. The results showed a high efficacy in the follow-up of patients with transitional cell carcinomas. Nevertheless, the specificity in case of urinary tract infection or hematuria limits the clinical significance [15, 16].

However, many tests (immunostaining of Lewis X, fibrin degradation products, p53, M344, BLC-4, telomerase activity, UBC, HA-HAase) are now under intensive investigation, but the value of all these tests is still insufficiently validated in diagnosis and follow-up [17].

Table 1. Comparison of six clinical studies of 5-ALA for the detection of bladder carcinomas

Authors	Number of patients	Number of biopsies	Enhanced tumor detection, %	Sensitivity %	Specificity %
Kriegmair et al. [24]	104	433	38	95.8	63.8
Jichlinski et al. [25]	34	215	76	89	57
Filbeck et al. [26]	55	130	18	87	59
Koenig et al. [27]	123	347	30.3	96	67
Riedl et al. [28]	52	–	25	94.6	43
De Dominicis et al. [29]	49	179	69	87	63

Furthermore, most of these tests are labor-intensive, and costs may limit their use as ancillary techniques in many institutions in daily routine [18].

Fluorescence Endoscopy

Cytoscopy in combination with the fluorescence phenomenon of malignant tumors appeared to be one of the most suitable methods for tumor detection during the last decade. Since the 60s urologists have sought for methods of in vivo labeling of neoplastic lesions, in order to decrease the risk of overlooking tumors, by means of an additional color contrast. But in vivo staining with tetracycline, methylene blue, fluorescein, or synthetic porphyrin compounds could not be established and has been abandoned [19–22].

Since 1992, 5-aminolevulinic acid (5-ALA) is investigated for fluorescence detection of urothelial cancer. 5-ALA is a precursor of the heme biosynthesis and induces an accumulation of fluorescent endogenous porphyrins, mainly protoporphyrin IX (PPIX), in tissues of epithelial origin. PPIX is the decisive dye for fluorescence detection with an excitation spectrum just above 400 nm. The fluorescence excitation is provided by an excitation light source (short-arc xenon lamp) with a specially designed dielectric short-pass filter (375–440 nm). Using this light source, the bladder can be examined under both white light and blue light. Following intravesical application of 5-ALA, a selective accumulation of PPIX in urothelial cancer could be demonstrated, providing an intensive color contrast between red-fluorescing malignant lesions and the non-fluorescing normal blue mucosa [23].

The results of 5-ALA fluorescence endoscopy (AFE), based on a biopsy-related evaluation, showed a significant increase in sensitivity for the diagnosis of neoplastic urothelial lesions such as dysplasias and carcinomas in situ as well as for the diagnosis of papillary tumors of additional evaluation of porphyrin fluorescence. The procedure was characterized by a sensitivity of 97% and a specificity of 65% [24]. Due to the topical administration of 5-ALA and the fast metabolism, only minor side effects such as urgency were observed in about 7% of the cases. The outstanding sensitivity of the procedure was confirmed by other investigators and ranges from 87 to 96% [24–29]. Table 1 summarizes the data published so far.

After these initial encouraging results using 5-ALA fluorescence endoscopy, the data recently have been validated in additional cases. In a cohort of 605 patients, 1,012 AFEs were carried out from 1995 until 2000 [30]. More than 50% of these patients presented with intermediate- and high-risk lesions or suffered from a recurrent disease. In total, specimens from 2,475 lesions were obtained. The mean biopsy rate was 2.4 per endoscopy. In 552 cases urothelial neoplasms had been found, 34% of these only due to their positive fluorescence. Table 2 shows the histopathological results of the 552 AFEs with malignant findings. The data demonstrate the superiority of AFE as compared with white-light endoscopy in case of high-risk urothelial lesions.

In order to investigate whether a 5-ALA-guided TUR is able to reduce the residual tumor rate, a randomized controlled phase III study was carried out. 165 patients with suspected bladder cancer were randomized into two treatment modalities. The follow-up resection was carried out after 10–14 days with white light. The percentage of patients rendered free from tumor at the first resection was defined as the principal parameter. The analysis of the data showed a significant advantage in favor of the AFE-controlled resection. 67.3% of the patients could be rendered free from tumors by means of an AFE-controlled resection. Under conventional conditions using white light, this proportion was only 46.9%. The number of patients with residual tumors after a first resection could thus be reduced by 40% [31].

Table 2. Histopathological classification of detected tumor lesions in 1,012 fluorescence endoscopies [30]

Histology	Detected with WLE (overlooked under AFE)	Detected with AFE (overlooked under WLE)	WLE and AFE
>pT1G2/3	–	5	37
pT1GIII	3	12	46
pT1GII	–	11	26
pT1GI	1	3	9
pTaGIII	–	5	11
pTaGII	11	19	80
pTaGI	32	60	178
pTxGIII	–	1	6
pTxGII	–	2	5
pTxGI	2	1	13
pTxGx	–	–	1
CIS	4	50	88
Dysplasia II	22	20	52
Total	75	189	552

WLE = White-light endoscopy; CIS = carcinoma in situ.

So far, data have proven that AFE: (1) enhances the sensitivity in the detection of neoplastic urothelial lesions, and (2) increases the radicality of TUR. Therefore, a decrease of the recurrence rate is expected together with an increase in the interval until recurrent disease takes place. First results have shown so far that there might be a significant influence on the early recurrence rates [32, 33]. Meanwhile, a prospective, randomized multicenter trial is in progress to evaluate the magnitude of the long-term effects of the fluorescence-guided resection as compared with the standard white-light approach.

Nevertheless, positive fluorescence is not limited to tumor lesions only. By traditional histology, 34.7% of the lesions that show specific PPIX fluorescence are histologically benign [30]. The diagnoses range from normal and hyperplastic urothelium to cystitis and squamous metaplasia. The questions that have to be posed are: (1) Does this result impair the positive effect of the technique, and (2) Is there a chance of false-positive lesions being partially preneoplastic lesions?

Starting with the latter, it has been shown that false-positive lesions such as simple hyperplasias have been known to already exhibit genetic changes identical to those of papillary tumors of the same patient [34]. The results obtained by fluorescence in situ hybridization and loss of heterozygosity analysis indicate that at least part of the false-positive lesions may have to be considered tumor precursors that are missed by conventional histology [35]. This aspect is currently investigated intensively in longitudinal and horizontal studies of biopsy material in order to evaluate systematically the genetic steps of tumorigenesis and their possible causal connection with a raised PPIX metabolism.

Furthermore, false-positive responses were frequently obtained from lesions with inflammation or scarring after prior TUR. This was evaluated by Filbeck et al. [36] who showed that the granulation tissue limits the procedure within 6 weeks after TUR. Such lesions are fluorescence positive, but apparently show a lower fluorescence intensity as compared with papillary tumors or even carcinomas in situ. Therefore, methods for fluorescence quantification or the additional use of autofluorescence have been established and are now under investigation in order to reduce the rate of false-positive biopsy specimens [37, 38].

Finally, the number of false-positive results seems to be acceptable, as in total the mean number of biopsies is low with 2.4 specimens per patient [30]. In this context, however, it is important to emphasize that white-light endoscopy and fluorescence endoscopy are complementary and not competing procedures. The concomitant investigation under blue light enhances the detection of malignant bladder lesions as compared with the standard white-light procedure alone.

Recently, D'Hallewin et al. [39] reported first clinical results with a new potent photosensitizer, hypericin. Hypericin is a hydroxylated phenanthroperylenequinone present in a number of plants and is widely distributed around the world. The hypericin-induced fluorescence showed high sensitivity and specificity in the detection of flat urothelial lesions without any side effects. The fluorescence excitation was performed with a xenon-arc lamp designed for the excitation of 5-ALA-induced PPIX fluorescence. However, larger trials are warranted to prove the diagnostic potential of this detection device.

Optical Sectioning

The above-mentioned limitations of standard endoscopy have led investigators to examine other methods of evaluating the bladder tissue. However MRI, CT scan, or transabdominal ultrasound are powerful techniques to assess distant metastases or large extended tumors of the bladder. Unfortunately, they failed in the detection of small papillary tumors or flat lesions, and their relatively low resolution prevents assessment of the degree of tumor invasion in the blad-

der wall. Therefore, recently new imaging devices based on the 'optical sectioning' of tissue have been investigated.

Optical coherence tomography has been developed in order to provide in situ high-resolution imaging of the bladder tissue. This is a technology which performs realtime, micron scale imaging (4–20 μm) near the level of histopathology. It is analogous to B-mode ultrasound, except that it uses infrared light as opposed to acoustic radiation. First experimental results suggest a procedure with a potential role envisioned in the management of transitional cell carcinomas, identifying the depth of infiltration noninvasively [40, 41].

Confocal laser scanning microscopy is a noninvasive modality for 'optical sectioning' of tissue. It allows imaging of the urothelium and parts of lamina propria and lamina muscularis throughout the bladder wall in vivo. This technique can image nuclear, cellular, and structural morphological features in thin sections with lateral and axial resolutions of 0.5–1 and 3–5 μm, respectively [42, 43].

Further basic and clinical research is necessary in order to prove the validity of this 'optical sectioning' in the diagnosis of bladder cancer.

Conclusions

During the last decade, several promising diagnostic techniques have been studied in order to improve the current diagnosis of superficial bladder cancer. However, the 5-ALA fluorescence endoscopy is now an established procedure. It has proven to be applicable and cost-effective, especially in the detection of high-risk flat lesions. A very promising concept could be the combination of an noninvasive specific marker, a detection device such as AFE, and 'optical sectioning' by optical coherence tomography or confocal laser scanning microscopy.

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