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Diagnosis and treatment options for bladder cancer: A review

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Abstract

Bladder cancer is the most frequent kind of urinary tract cancer. We will look at the most recent breakthroughs in the diagnosis and treatment of this illness in this review. The most significant tools in the diagnosis and follow-up of bladder cancer are cystoscopy and urine cytology. Several options have been examined, either to minimise the frequency of cystoscopy or to increase its sensitivity for tumour identification. Urine-based markers and point-of-care testing are examples of this. When compared to routine resection under white light, narrow-band imaging and photodynamic diagnosis/blue-light cystoscopy have showed promise in improving identification and minimising recurrence of bladder tumours by enhancing bladder resection completeness. The majority of individuals diagnosed with bladder cancer for the first time have non-muscle-invasive disease, which necessitates adjuvant intravesical chemotherapy and/or immunotherapy. The latest advancements in intravesical post-resection regimens are presented. Both laparoscopic radical cystectomy and robot-assisted radical cystectomy have been proven to minimise peri-operative morbidity while being oncologically equal to open radical cystectomy in the medium term for patients with muscle-invasive bladder cancer. Bladder-preserving methods include resection and chemoradiation, and in certain cases, they are as effective as surgery. These novel techniques are also examined in terms of their development, benefits, and drawbacks.

Keywords: Bladder cancer; Cystoscopy; Narrow-band imaging; Photodynamic Diagnosis; Radical cystectomy; Urinary markers

1. Introduction

Bladder cancer is the most prevalent cancer of the urinary system, with a four-fold greater incidence in males than in women [1]. In the last 5 to 10 years, a lot has changed in terms of bladder cancer detection and treatment. Surprisingly, death rates in Europe appear to have decreased over the last decade, by about 16 % in men and 12 % in women [2]. Although cystoscopy is still an important method for detecting and monitoring bladder cancer, tiny papillary tumours or carcinoma in situ (CIS) can be overlooked by normal white-light cystoscopy (WLC), which can lead to early recurrence. As a result, innovative methods such as narrow-band imaging (NBI) cystoscopy and photodynamic diagnostics (PDD) have been developed [3]. Several molecular urine assays have been developed throughout the years to aid in the identification of bladder cancer. Despite their initial promise, none have proven to be sensitive or specific

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enough to avoid cystoscopic monitoring [4]. These new components of diagnosis will be examined in more detail in the following sections.

About 75 to 85 percent of patients will have non-muscle invasive bladder cancer (NMIBC), often known as'superficial' bladder cancer, which is illness restricted to the mucosa (Ta) or submucosa (T1). Adjuvant intravesical chemotherapy and/or immunotherapy are required for NMIBC. The kind and quantity of intravesical instillations used are determined by a variety of parameters, including the tumor's grade, stage, multifocality, and tolerability. The chance of NMIBC recurrence is high, and the risk of advancement is varied. Muscle invasion is a high-risk complication of CIS (tumour in situ; Tis). Radical cystectomy should be used to treat CIS and T1 disease that is resistant to bacille Calmette-Guérin (BCG) immunotherapy, high-grade recurring T1 disease, muscle-invasive bladder cancer (MIBC) (stage >T2), or high-volume disease that cannot be handled endoscopically [5]. Laparoscopy has been developed as a minimally invasive cystectomy approach [6,7]. Bladder-preservation techniques for MIBC appear to be successful therapies as well, and can be as effective as drastic surgery with careful patient selection [8]. This article will discuss current advancements in the detection and treatment of bladder cancer that is not metastatic.

2. Classification

It is crucial to classify bladder cancer in order to select the best treatment plan and anticipate results. The WHO grading system for bladder cancer changed in 2004, incorporating a variety of histologic descriptions such as urothelial papilloma (completely benign lesion), papillary urothelial neoplasm of low malignant potential (PUNLMP), and low-grade and high-grade cancer, rather than the previous three grades of well (G1), moderately (G2), or poorly differentiated (G3) papillary urothelial carcinoma [9,10]. The TNM (tumour, node, metastasis) classification has remained mostly unchanged since the last report in 2009 [11], with some minor alterations to the nodal categorization.

3. Diagnosis

3.1. Cystoscopy

For decades, standard WLC has been used to identify and resect bladder cancers. With the goal of minimising disease recurrence and progression, new technologies have been created to improve the quality of cystoscopy and transurethral resection of bladder tumour (TURBT) that is now achieved.

3.2. Photodynamic diagnosis/blue-light cystoscopy

PDD increases the likelihood of detecting subtle bladder cancer. The dye 5-aminolevulinic acid (5-ALA) or its hexyl ester hexaminolevulinate is injected into the bladder and absorbed by dysplastic tissue, allowing photosensitization to occur. Under blue reference light, the aberrant tissue exhibits a red colour. The colour of normal tissue is blue. PDD is advised to help diagnosis during first TURBT, in patients with positive urine cytology but negative WLC findings, and for the assessment of tumour recurrences in individuals who have never had PDD done before. It is also advised for individuals with CIS or multifocal tumours during their initial follow-up [12]. Blue-light cystoscopy (BLC) identifies more bladder cancers than WLC, including more high-risk tumours, according to a meta-analysis and systematic review. BLC with 5-ALA given at the time of TURBT promotes a more complete resection and prolongs recurrence-free life, according to four randomised controlled trials (RCTs) demonstrating clinical efficacy. However, the method of administering adjuvant intravesical treatment differed throughout the four RCTs examined, potentially reducing the benefit of PDD [13]. PDD has yet to be proven to stop progression or enhance survival.

3.3. Narrow-band imaging

Without the use of dyes, NBI cystoscopy increases the fine structure of the bladder mucosal surface. Light with longer wavelengths can penetrate further. Unlike BLC, which needs the instillation of photosensitizing chemicals through a urethral catheter prior to surgery, NBI cystoscopy does not require any further invasive measures. It can also be done with a flexible cystoscope, making it easier to do in an outpatient situation. NBI cystoscopy had a lower false-positive rate than normal WLC in detecting recurrent NMIBC [14]. At one year, TURBT with NBI lowers the incidence of NMIBC recurrence by at least 10% [15]. There haven't been any clinical trials that compare NBI cystoscopy to WLC or BLC yet.

3.4. Urinary markers

Cytology is the most extensively used non-invasive urine test, with strong specificity and sensitivity for detecting high-grade malignancies but limited sensitivity for low-grade tumours [16] and a delay in results availability. Several urine indicators have been studied in the hopes of lowering cystoscopy frequency [4]. Several are commercially accessible,

but because to low sensitivity and/or cost, none have been integrated into the standard of care. In circumstances when urine cytology is ambiguous, these markers may be used as a supplementary diagnostic test.

Fluorescence in situ hybridization (FISH) can be used to discover chromosomal abnormalities in urine cells that are associated with a diagnosis of bladder cancer. One commercial test, for example, employs fluorescently labelled DNA probes to identify aneuploidy in chromosomes 3, 7, and 17, as well as deletion of the P16 tumour suppressor gene's 9p21 locus. [17]. FISH surpassed cytology in most comparative investigations across all stages and grades of bladder cancer [18-20]. However, because the test has a high false-positive rate and is costly, FISH results should only be utilised when urine cytology results are ambiguous.

Another marker that can be seen in empty urine is nuclear mitotic apparatus protein (NMP)-22. The US Food and Drug Administration has authorised a point-of-care tumor-marker test for bladder cancer monitoring. Very few tumours were missed in individuals who had negative findings for both cystoscopy and the NMP-22 Bladderchek test, and cytology provided no further diagnostic information [22]. The use of NMP-22 did not aid clinical decision-making in cases where physicians would perform a cystoscopy even if there was a low risk of progression (1%) or recurrence (5%) [23]. However, if the progression and recurrence thresholds were increased to 3% and 8%, respectively, NMP-22 could help distinguish which patients would need cystoscopy or not.

4. Treatment

4.1. Non-muscle invasive bladder cancer

For patients with NMIBC, TURBT is the first-line therapy. Unfortunately, adjuvant therapies are required due to the high rate of recurrence and progression following TURBT [5, 24, 25]. Instillation of chemotherapeutic medicines, such as mitomycin-C (MMC), or immunotherapeutic agents, such as BCG, either alone or in different combinations, is required. Although the method is severely underused [27], a single dose of intravesical chemotherapy given after TURBT but on the same day dramatically decreased the likelihood of tumour recurrence by 39 percent in patients with tumours with a low risk of recurrence and progression [26]. The conventional treatment for high-grade NMIBC and CIS is intravenous BCG, which should be administered on a regular basis [28]. Unfortunately, some patients cannot tolerate hematuria or irritative lower urinary-tract symptoms and/or are resistant to therapy.

4.2. Bacille Calmette-Guérin treatment and electromotive drug administration of mitomycin C

In patients with high-risk superficial bladder cancer, Di Stasi et al. found that intravesical, sequential BCG followed by electromotive administration (EMDA) of MMC (EMDA-MMC) resulted in a longer disease-free interval, lower recurrence and progression rates, and improved overall survival (OS) and disease-specific survival (DFS) rates when compared to BCG alone. The treatment plan included a 9-week induction period that included two weekly BCG instillations and one weekly EMDA-MMC instillation, which was repeated three times. If patients were disease-free after three months, they were put on a monthly maintenance plan, taking EMDA-MMC for two months, then BCG for one month, and repeating the cycle three times [29]. BCG-induced inflammation, according to the scientists, may improve the permeability of the bladder mucosa, allowing MMC to more easily enter the target area and exercise its anticancer impact. The same group recently shown that intravenous EMDA-MMC before TURBT is practical and safe. In comparison to TURBT alone or intravesical passive diffusion of MMC following TURBT, it lowered recurrence rates and increased the disease-free time [30]. However, no other institution has been able to duplicate these findings. In 2009, a hospital made sequential BCG/EMDA-MMC standard treatment implicated for high-risk NMIBC. 10 out of the 62 individuals treated did not react to therapy. Twenty-one of the remaining 52 patients have completed the 12-month follow-up, and 17 of them are still disease-free [31].

4.3. Hyperthermic mitomycin C

Endoscopic and histological examination have showed that a combination of intravesical MMC and microwave-induced bladder wall hyperthermia (HT) for Ta/T1 bladder cancer was first established in 1995, and this combination can produce necrosis of transitional cell tumours [32]. Since then, a small RCT comparing MMC-HT to MMC alone has revealed a considerably improved 10-year DFS rate [33]. When MMC-HT was given instead of MMC alone, a systematic review found a 59 percent reduction in NMIBC recurrence; however, this study was hampered by the small number of RCTs available for inclusion. MMC-HT may become the standard therapy in the future for high-risk patients with recurring tumours, patients who are unsuitable for radical cystectomy, and patients for whom BCG treatment is contraindicated, according to the authors [34].

4.4. Intravesical gemcitabine

The chemotherapeutic drug gemcitabine was recently approved for the treatment of metastatic bladder cancer [35]. Intravesical gemcitabine administration for NMIBC has been studied and shown to be safe with a manageable adverse effect profile. Because of the diverse patient groups, a Cochrane assessment of the existing evidence base of randomised trials was restricted. Patients with high-risk NMIBC who received intravesical gemcitabine had a higher risk of recurrence and progression than those who received BCG; however, high-risk BCG-refractory patients who received intravesical gemcitabine had fewer recurrences than those who received BCG. Rather than a single injection after surgery, many doses would be necessary [36]. In patient's refractory to BCG, the South-West Oncology Group is now testing gemcitabine (6-weekly instillations followed by monthly maintenance for 12 months). Only 28% of evaluable patients exhibited a sustained response after a year [37].

4.5. Muscle-invasive bladder cancer &minimally invasive techniques in radical cystectomy

The current gold-standard therapy for MIBC and high-risk recurrent NMIBC is open radical cystectomy (ORC). All MIBC patients should, ideally, undergo platinum-based neoadjuvant treatment [38,39]. The peri-operative complication rate for ORC ranges from 25 to 62 % [40]. As a result, less invasive radical cystectomy approaches have been investigated.

Cohort studies make up the majority of the known data. Lower blood loss, reduced surgical discomfort, early recovery of bowel function, and a shorter hospital stay are all benefits of laparoscopic radical cystectomy (LRC) [6,41]. Given the problem of selection bias in most series, the data should be evaluated with caution. In large cohorts with up to 5 years of follow-up, recent data shows that LRC has favourable early oncologic outcomes with minimal morbidity [42]. Nonetheless, as compared to ORC, LRC is considered an advanced laparoscopic technique since it involves numerous challenging procedures and has fewer degrees of freedom of movement.

In 2001, a new minimally invasive surgical system was launched. Binocular three-dimensional high-definition endoscopic vision improves the view of the operation field. The motions of the human hand can be replicated by 'Endowrists' on the tip of each instrument. In a limited RCT comparing robot-assisted radical cystectomy (RARC) to open radical cystectomy (ORC), Nix et al. found that RARC reduced surgical blood loss, time to regain bowel function, and analgesic needs when compared to ORC, with equal lymph-node (LN) yields [7]. A prospective cohort study found that after 30 and 90 days after RARC, there were fewer significant complications than with ORC [43]. RARC has a positive short-term result, with an OS rate of 70 to 90 percent after 2 to 3 years of follow-up [44-47]. The International Robotic Cystectomy Consortium is made up of 18 institutions that have demonstrated LN yields and positive surgical margin rates that are equivalent to ORC [48,49]. On their collaborative database, 1,200 cystectomies have been documented to far [50].

The cystectomy and LN dissection should be done intracorporeally, with extracorporeal urine diversion via a lower midline incision, according to most urologists doing LRC or RARC. With further expertise, intra-corporeal restoration of urine diversion, whether via ileal conduit or orthotopic neobladder production, has become possible. Clearly, there is a severe learning curve. Although operation durations are longer, patients use less inpatient narcotics and have similar short-term therapeutic results to extracorporeal diversion [51-53].

However, RCTs comparing RARC and ORC are in short supply. Several trials are currently underway, including the randomised CORAL (Randomized Control Trial of Open, Robotic, and Laparoscopic Radical Cystectomy) trial [54], the OVRACT (Open Versus Robotic-Assisted Radical Cystectomy: A Randomized Trial) trial [55], and the BOLERO (Bladder Cancer: Open Versus Laparoscopic or Robotic Cystectomy) trial at Cardiff University, UK [56]. In the next 1 to 2 years, the long-term results of the first cohort of RARC patients should be accessible.

4.6. Bladder preservation

Bladder preservation strategies have also been researched. A phase III study found that combining chemotherapy (fluorouracil with mitomycin) with radiation improved the 2-year DFS rate and lowered the salvage cystectomy rate, with satisfactory long-term bladder function [8]. Long-term data from Massachusetts General Hospital in the United States has shown that after maximal TURBT, combined multi-modal therapy in the form of concurrent cisplatin-based chemotherapy and radiotherapy achieves complete response and preserves the native bladder in more than 70% of patients, with long-term survival rates comparable to current cystectomy series [57]. However, because this centre employed a variety of different procedures, the best treatment regimen is yet unknown. However, these findings imply that in some individuals with muscle-invasive illness, this method might be a viable alternative to drastic surgery.

5. Conclusion

In recent years, a number of novel procedures and advances have been launched to help with the diagnosis and treatment of bladder cancer. Enhanced cystoscopy has been made possible by technological advancements, with BLC enhancing the identification of bladder cancers and improving the quality of tumour excision. Despite the fact that numerous forms of urine indicators have been investigated, none have yet shown to be sufficiently specific or sensitive to substitute routine cystoscopic surveillance of NMIBC. MMC-HT, BCG in conjunction with EMDA-MMC, and intravesical gemcitabine have all been studied as intravesical treatments for NMIBC. Over the last ten years, minimally invasive radical cystectomy has grown in favour. The quality of available data for these emerging surgical methods will be improved by the outcomes of coordinated worldwide initiatives and randomised trials, which are widely awaited. ORC remains the gold-standard therapy for MIBC while the long-term advantages of RARC are still being studied. For individuals who want to keep their bladders, TURBT with a combination of chemotherapy and radiation has demonstrated to be as effective as major surgery in some cases.

Abbreviations

- BCG: bacille Calmette-Guérin
- LRC: laparoscopic radical cystectomy
- MIBC: muscle-invasive bladder cancer;
- MMC: mitomycin C
- MMC-HT: mitomycin C with hyperthermia
- NBI: narrow-band imaging
- NMIBC: non-muscle-invasive bladder cancer
- ORC: open radical cystectomy
- RARC: robot-assisted radical cystectomy
- RCT: randomized controlled trial

Compliance with ethical standards

Disclosure of conflict of interest

No Conflict of interest.

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