Curr Urol Rep (2017) 18: 34
DOI 10.1007/s11934-017-0680-0

Transurethral Resection of Bladder Tumors: Improving Quality Through New Techniques and Technologies

Daniel Zainfeld[1] · **Siamak Daneshmand**[1]

Published online: 10 March 2017

Abstract
Purpose of Review Cystoscopy with transurethral resection of bladder tumors (TURBT) is essential in the diagnosis of bladder cancer as well as the management of non-muscle-invasive disease yet remains a comparatively imprecise procedure secondary to variability among patients, tumors, and surgeons alike. We will review evolving technologies and techniques used to enhance safety and efficacy of TURBT performance and education in the management of bladder cancer.
Recent Findings Though a generally safe procedure, efficacy of TURBT in terms of complete tumor excision, appropriate pathologic diagnosis, and absence of complications can vary significantly with direct impact on patient outcomes. Application of new techniques including bipolar electrocautery and photodynamic enhancement continues to shape endoscopic management of bladder cancer and improve safety, tumor excision rates, and downstream outcomes.
Summary High-quality bladder tumor resection is essential for effective bladder cancer management. Technologies such as bipolar electrocautery and photodynamic visualization improve safety and tumor eradication. Improved education and surgical technique will further standardize high-level outcomes for patients undergoing TURBT.

This article is part of the Topical Collection on *Minimally Invasive Surgery*

✉ Siamak Daneshmand
daneshma@med.usc.edu

Daniel Zainfeld
zainfeld@med.usc.edu

[1] USC Norris Comprehensive Cancer Center, 1441 Eastlake Avenue, Suite 7416, Los Angeles, CA 90089, USA

Keywords Bladder cancer · Monopolar · Bipolar · Transurethral resection · Blue light

Background

Urothelial carcinoma (UCC) is the fourth most common malignancy among men in the USA. While somewhat less common among women, it accounts for almost 77,000 new cases and 16,000 deaths annually [1]. Despite growing application of novel systemic therapies for the treatment of advanced disease, notably in the realm of immunotherapy, endoscopic resection remains the mainstay of initial diagnosis, staging, and in non-invasive disease treatment.

Edwin Beer published the first report involving the application of electric current endoscopically through a cystoscope for the fulguration of otherwise inoperable papillary tumors of the bladder in 1910 [2]. This initial work was completed in a water medium, a requirement which would persist for decades. The myriad potential applications of endoscopic cauterization and transurethral resection of bladder tumors (TURBTs) were quickly recognized and are now well-established in the delivery of urologic care for both benign and malignant conditions. In the management of UCC in particular, transurethral resection (TUR) remains the most essential aspect of diagnosis, as well as management in non-invasive disease.

Bladder cancer most commonly presents in the form of hematuria, gross or microscopic, prompting cystoscopic evaluation [3]. While various urinary diagnostic tests have been developed to facilitate identification and diagnosis of UCC with some success, TURBT in conjunction with bimanual exam is the key procedure in establishing pathologic diagnosis and clinical stage. Virtually all urologic and cancer society guidelines stress the importance of TUR for this purpose

[4–6]. Specifically, complete visualization of the entire bladder and resection of all visualized tumors is recommended when technically feasible [6]. Approximately 75% of patients present with non-muscle invasive disease in which cancer involves only the urothelium (Ta/CIS) or lamina propria (T1) without invasion to the detrusor muscle (T2) [7]. Recurrence is common among patients with non-invasive bladder cancer. Analysis of 2596 patients from seven European Organization for Research and Treatment of Cancer (EORTC) trials demonstrated probabilities of recurrence ranging from 15 to 61% and progression rates of less than 1 to 17% dependent on a number of clinical and pathologic factors including tumor quantity, size, and grade among others [8]. Differentiating recurrent tumors from those not initially identified or incompletely resected is difficult. Recent advancements in visualization of tumors through application of technologies for optical enhancement at time of resection as well as evolving practice patterns with regards to repeat resection of high-risk tumors have highlighted the importance of initial resection on staging and tumor recurrence. Costs attributed to bladder cancer are substantial with significant sums accrued in the setting of non-invasive disease due to greater prevalence and protracted course [9]. As such, optimization of tumor resections carries significant implications not only for oncologic care but patient factors including need for additional procedures, quality of life, and overall cost of care.

TURBT is a safe procedure with minimal morbidity overall, often performed in the outpatient surgery setting. Complication rates are approximately 4–6% of which urinary tract infections and significant hematuria are most common. Despite the general low rate, complications of TUR remain significant due to the frequency with which it is performed [10•, 11]. Resection of bladder tumors is approached with two procedural goals. First, identification and eradication of all cancer within the bladder dependent on adequate visualization of cancerous tissues and technical skills for complete resection. Second, provision of adequate tissue sampling for correct pathologic diagnosis is essential. In the setting of high grade cancer, this generally entails depth of resection to include detrusor muscle in order to facilitate evaluation of tumor stage. Resected tumors should be examined by a pathologist for assignment of World Health Organization (WHO) grade (high vs low) and determination of depth of invasion. These factors allow for appropriate prognostication and guide further treatment decisions. Failure to achieve either of these aims results in detrimental effects for patients in the form of increased recurrence, incorrect diagnosis, and need for additional procedures. Developments in both technology and technique have expanded the safety and efficacy of endoscopic resection as an effective tool in the assessment and management of UCC and continue to build upon those principles first suggested in the early 1900s.

Bipolar Electrocautery

Endoscopic resection using monopolar electrocautery has been extensively used and evaluated since introduction in the early 1900s [2]. Following more recent introduction, bipolar electrocautery has been widely adopted for transurethral resection of the prostate (TURP) in the setting of benign enlargement and obstruction. The primary advantage of bipolar energy in this setting derives from the ability to resect in an isotonic fluid medium (e.g., saline) as opposed to water, glycine, or other common resection mediums. Bipolar electrocautery, through completion of an electric circuit utilizing only the resection loop and sheath of the device itself, bypasses the need for patient inclusion in the electric circuit obviating the need for electrolyte free fluid mediums and allowing for lower energy systems. For patients undergoing TURP, bipolar resection has virtually eliminated risk of transurethral (TUR) syndrome, a rare but serious complication and allowed for extended resections with better perioperative outcomes in urinary symptoms without increase in early or late complications such as clot retention and bladder neck contracture [12–15]. Given the improved safety profile and indications of comparable, if not superior, outcomes in the management of obstructive prostatic hyperplasia, bipolar electrocautery has been quickly adopted for use in management of bladder cancer as well.

Early reports indicated safety and oncologic efficacy of bipolar resection of bladder tumors without increased incidence of TUR syndrome, obturator jerks, bladder perforations, or other complications [16, 17]. Prospective studies have supported these conclusions. Xishuang et al. compared outcomes among monopolar, plasmakinetic (bipolar), and holmium laser in the management of non-muscle invasive bladder cancer (NMIBC) among 173 patients divided between the three techniques. Bipolar and holmium laser groups had significantly decreased the occurrence of obturator nerve reflex, bladder perforation, bladder irritation, postoperative irrigation, catheterization time, and hospitalization time without difference in recurrence rates at 2 years (45.1% monopolar, 37.5% bipolar, and 31.7% holmium, $p = 0.343$) [18]. Similar prospective randomized studies have supported equivalence between the two techniques in complications including thermal effects, obturator reflex, bladder perforation or injury, postoperative hemoglobin levels, and postoperative sodium levels [19, 20, 21•]. Sugihara et al. retrospectively assessed outcomes among patients with clinical T2 or less disease undergoing TURBT with monopolar or bipolar electrocautery. After one-to-one propensity score matching, procedures using bipolar resection had significantly lower incidence of complications (4.6 vs 5.8%, OR 0.78) including bladder injury (0.3 vs 0.6%, OR 0.57) while no differences in hemostasis, transfusion, or anesthesia duration were noted suggesting benefits to bipolar use for TURBT beyond the equivalent outcomes initially described [22]. Due to quick proliferation and

Table 1 Trials comparing monopolar and bipolar TURBT

Reference	Study design	Total patients enrolled	Key findings
Xishuang et al. [18]	Prospective, randomized comparison of monopolar, bipolar, and holmium laser resection of NMIBC	173	No significant difference in recurrence at 2 years (45.1% monopolar, 37.5% bipolar, and 31.7% holmium, $p = 0.343$). Decreased incidence of obturator nerve reflex, bladder perforation, catheterization time, and hospitalization time among bipolar and holmium laser groups in comparison to monopolar.
Del Rosso et al. [20]	Single center prospectively randomized comparison of resections for primary non-muscle invasive bladder cancer	132	Mean catheterization time and hospital stay favoring bipolar technique. Mean operative time 27 min bipolar vs 31 min monopolar. Median time to tumor recurrence 12.4 vs 11.9 months in bipolar and monopolar, respectively.
Mashni et al. [19]	Prospective evaluation of patients undergoing monopolar or bipolar resections including blinded pathologic analysis and clinical outcomes	83	No significant clinical differences between resection methods (perforation, obturator reflex, need for catheterization, admission). Thermal artifact similar between modalities (23.7 vs 24.4%) with slightly less distortion among bipolar specimens
Venkatramani et al. [21•]	Single center randomized controlled trial analyzing safety and efficacy of bipolar resection for patients with suspected bladder tumors	147	No statistically significant differences in obturator jerk, decrease in hematocrit, transfusion, bladder perforation, or resection time. Significantly lower incidence of severe cautery artifact in bipolar arm (25 vs 46.7%, $p = 0.0096$)
Sugihara [22]	Retrospective analysis of outcomes from patients undergoing monopolar or bipolar TURBT at 788 Japanese hospitals with one to one propensity score matching	8188 pairs generated	Bipolar resection associated with lower incidence of severe bladder injury (0.3 vs 0.6%, OR 0.57) and other complications (4.6 vs 5.8%, OR 0.78). No reported differences in requirement of postoperative hemostasis procedures, transfusion, or duration of anesthesia

adoption among urologists, a number of additional trials have been completed. A recent meta-analysis including six randomized controlled trials found bipolar TURBT to be associated with shorter operative time, less blood loss, shorter catheterization time, decreased obturator nerve reflex, and decreased incidence of bladder perforation in comparison to traditional monopolar procedures. In addition, a decreased rate of tumor recurrence was noted at 2 years [23]. While the physiologic mechanisms of some of these results are unclear, little question remains regarding the safety profile of bipolar resection for both bladder tumors and benign prostatic tissue.

In addition to safe excision, pathologic analysis of specimens is essential for the correct assignment of tumor grade and stage. Cautery artifact secondary to thermal damage in the process of resection is known to impact specimen quality and pathologic interpretation [24]. Wang et al. performed a blinded pathologic comparison of 11 TURBT specimens obtained from monopolar resection and 11 from bipolar resections. While bipolar chips were noted to be smaller secondary to a smaller resection loop, no significant pathologic differences were noted between specimens including no difference in cautery artifact or ability to provide diagnosis [25]. A similar study including 25 patients demonstrated no qualitative differences between groups in extent of histologic thermal artifacts with mean depth of thermal artifact 0.237 mm in the bipolar group and 0.26 mm in the monopolar group ($p = 0.8$) with appropriate diagnosis and adequate staging in all specimens [24]. In prospective analysis of 83 patients, pathologic examination revealed tissue distortion from thermal artifact making specimens unreadable within 11/38 (28.9%) monopolar and 7/45 (15.6%) bipolar specimens, suggesting less tissue distortion and potential for improved staging and grading of bladder tumors with bipolar resection techniques (Table 1). Venkatramani et al. also reported incidence of severe cautery artifact as a secondary outcome in a large, prospective randomized trial finding significantly decreased occurrence (25 vs 46.7%, $p = 0.0096$) in the bipolar arm [21•].

The safety of bipolar electrocautery for the resection of bladder tumors is established. Further study will better define potential benefits in comparison to monopolar electrocautery.

However, given promising results of early evaluations, establishment of bipolar TURBT appears well justified.

Enhanced Cystoscopy

The importance of complete resections in the setting of non-invasive and even invasive disease has been demonstrated, particularly when high-grade disease is initially identified. In fact, repeat resection for high-grade tumors or those involving the lamina propria (cT1) are uniformly recommended within 4–6 weeks of initial resection due to the high incidence of pathologic understaging and the frequency of residual tumor [6, 26]. A recent study by Gendy et al. examined residual cancer and up-staging rates in a contemporary Australian cohort and found residual tumor in 56.8% of initial high-grade Ta tumors and 39.6% of T1 lesions. After repeat resection, 14.6% of patients with T1 disease and 2.7% of those with high grade Ta (non-invasive) disease were upstaged to muscle invasive category (cT2), significantly impacting prognosis and treatment [27]. These data are in concordance with a body of literature reflecting the essential nature of complete tumor eradication and adequate tissue for staging [27–32]. The impact of restaging TUR in high-risk bladder cancer has been demonstrated to decrease recurrent tumor at first cystoscopy as well as future progression rates indicating the value of more complete tumor eradication [29, 33].

Among the most exciting developments in endoscopic resection has been the implementation of photodynamic aids to enhance intravesical tumor visualization. The key limitation in the endoscopic management of early-stage bladder cancer is the inherent difficulty of identifying all areas of malignancy within the bladder due to the multifocal nature of bladder cancer and often inconspicuous, yet significant, lesions characteristic of carcinoma in situ (CIS) with standard visualization techniques [34]. Photodynamic diagnosis seeks to improve tumor visualization by enhancing differentiation of normal urothelium and neoplastic tissue. Fluorescence cystoscopy, commonly termed blue-light cystoscopy (BLC), is the most validated technique for enhanced visualization. BLC requires preoperative bladder instillation of a photosensitizing agent, most commonly hexyl aminolevulinic acid, which is absorbed disproportionately by malignant cells and emits a distinct red fluorescence when exposed to blue light (380-480 nm) (Fig. 1) [35, 36]. Licensed in Europe in 2005, a growing body of literature has demonstrated efficacy through greater tumor detection and successful resection with downstream effects on cancer recurrence and costs of care. In 2007, Fradet et al. reported outcomes from 196 patients who were prospectively evaluated with both standard white-light and blue-light illumination at time of resection. Identified lesions were mapped and biopsied with CIS specifically found in 113 lesions involving 58 patients. Blue-light illumination provided greater identification of these CIS lesions 104 (92%) compared to standard white light which identified just 77 (68%) [37]. A subsequent prospective randomized study examined the impact of blue light cystoscopy on cancer recurrence by randomizing 814 patients with suspected bladder cancer to TURBT with standard white light or with the addition of blue light evaluation and resection. Sixteen percent of patients with Ta or T1 disease had at least one lesion identified only by blue light cystoscopy. Most impressively, at 9 month follow-up, tumor recurrence was significantly decreased following blue light resection (47 vs 56%, $p = 0.026$) [38]. Long-term follow-up reported for this cohort subsequently demonstrated durable benefits as 38% of those in the blue light group remaining tumor free in comparison to 31.8% in the standard group at greater than 50 months post-procedure. Of those recurring, median time to recurrence was significantly greater in the fluorescence group (16.4 vs 9.4 months, $p = 0.04$) [39••]. Two meta-analyses verify the significantly increased detection of both papillary tumors and CIS by addition of blue light while reducing residual disease rates and recurrence rates at extended follow-up [40, 41•]. Cost concerns are prevalent in the introduction of any new technology and must be evaluated in context of clinical benefits. Witjes et al. examined costs over time with application of BLC finding a higher initial cost of blue-light cystoscopy but decreased costs overall due to fewer repeat procedures required in light of less recurrence [42].

Alternative to fluorescence cystoscopy, narrow band imaging (NBI) has emerged as a viable tool for improved tumor visualization that circumvents the requirement for preoperative bladder instillation of a photosensitizing agent. Optical filters reduce light to blue (415 nm) and green (540 nm) components which are well-absorbed by hemoglobin and allow highly vascular malignant lesions to be visualized more easily in contrast to surrounding mucosa (Fig. 2) [36]. NBI, though not as extensively studied or validated as BLC, has been demonstrated to similarly improve tumor detection and in some series, recurrence free survival rates. A prospective trial examining patients with NMIBC randomized subjects to NBI TUR or standard white light and found TUR performed with NBI reduced recurrence significantly at 1 year (32.9 vs 51.4%, OR = 0.62; $p = 0.0141$) [43]. More recently, 12-month outcomes were reported for a prospective randomized multicenter study comparing TURBT for NMIBC with or without NBI. No significant difference was noted in recurrence rates at 12 months (27.1% white light and 25.4% NBI; $p = 0.585$) though among a subset of patients deemed low risk for recurrence, those undergoing NBI-assisted resection had decreased recurrence (5.6 vs 27.3%; $p = 0.039$) [44]. Further study of narrow band imaging will better define its role and potential advantages in the management of bladder cancer.

The value of photodynamic enhancement and BLC in particular for improving endoscopic resection is clear and represents a tremendous advance in the management of early stages of bladder cancer. Opportunities for improvement remain as

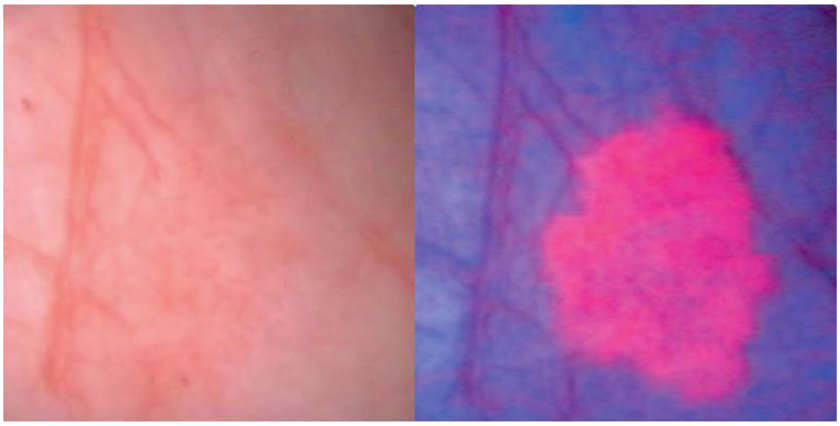

Fig. 1 Tumor appearance with white light cystoscopy (*left*) vs blue light enhancement (*right*)

some cancerous lesions continue to escape visualization despite enhanced visualization [37]. BLC is also associated with a 12% false positive rate, resulting in resection of additional healthy tissue and potential associated morbidity though this is comparable to reported false positives with standard white light cystoscopy [35, 45].

Education

A growing body of evidence points to the variability in tumor resection quality with direct impact on patient care even beyond the critical component of tumor visualization. In addition to individual patient and tumor characteristics, surgeon education, experience, and surgical resection technique impact resection quality. Though simple in aspects of anatomic and procedural complexity, complete endoscopic resection of bladder tumors requires significant technical skill which must be applied uniquely to individual patients dependent on tumor size, location, quantity, and other anatomic factors to achieve complete tumoral excision and appropriate pathologic diagnosis, i.e., "high quality" TURBT.

In order to better characterize variability in endoscopic resections, researchers have evaluated potential sources of subpar outcomes including patient factors, tumor characteristics such as grade, size and number, and surgeon factors including experience or training level through their effects on surgical outcomes. As sampling of the detrusor is a requisite goal in this population, it is commonly evaluated as a surrogate for quality of resection. Bos et al. recently completed a retrospective review of 463 TURBTs to determine if resident involvement impacted outcomes from TURBTs for bladder cancer finding specimens were significantly less likely to contain detrusor muscle among high-risk patients ($p = 0.006$) [46•]. Huang et al. reported similar findings among 216 patients deemed to have undergone complete endoscopic resection of bladder tumors. In addition to "junior surgeon" category, tumor size, and tumor location including lateral, dome, and anterior tumors were associated with absence of detrusor muscle in the specimen [47]. These studies were in agreement with Mariappan et al., who demonstrated large tumor size, high

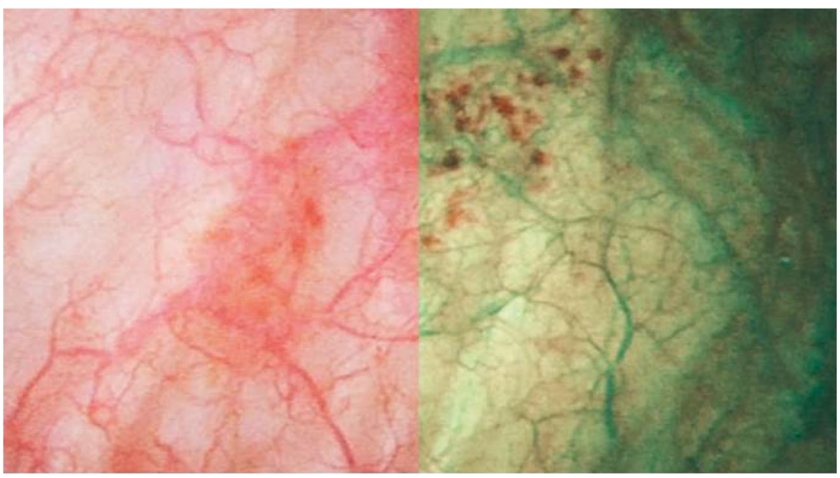

Fig. 2 Narrow band imaging (*right*) enhances visualization of vasculature and tumor in comparison to white light (*left*)

grade pathology, and surgeon experience (year 5 trainee or higher) to be independently associated with the presence of detrusor muscle in TUR specimen. Both absence of detrusor muscle and resection by junior surgeons were associated with an increased recurrence rate at first follow-up cystoscopy [48]. Conversely, Shoshany et al. examined a similar subset of patients who had undergone complete resection of bladder tumor and found surgeon experience and tumor location had no correlation with likelihood of detrusor muscle in the specimen while higher clinical stage, tumor grade, and extent of disease were associated with the presence of detrusor muscle (OR 1.8–3.2) [49]. Reasons for this discrepancy are unclear but could certainly involve training environment, supervision, and educational techniques. The impact of surgical duration of TURBT on postoperative complications was recently examined as well. An increase in complications was noted with greater operative duration despite controlling for various patient health factors [10•]. A key limitation in this study is inability to account for surgeon experience or training level as these factors may directly contribute to operative times. Surgical education remains a challenging arena as concerns for patient care, safety, and procedural efficiency and efficacy must be balanced with teaching of junior surgeons. Simulations offer a new avenue of instruction prior to patient care and continue to be explored in many procedures including TURBT but have not matured to practice at this time [50, 51]. Evaluation of an educational tool, the Simbla Transurethral Resection of Bladder Tumor simulator, recently found it to serve as a feasible complement to surgical education based on training needs analysis suggesting promising developments on the horizon [52].

At our institution, we have found that an "intermittent resection technique" allows trainees to accommodate to TUR instrumentation and procedure while maintaining control and limiting complications. This technique can be clearly visualized in a previously published video presentation [53•]. Rather than passing the resection loop in single large swipes which afford limited opportunity for feedback and adjustment, resections are made in a series of intermittent cuts. In this way, depth and direction of resection are adjusted based on feedback from supervising surgeons with each tumor. We have found no increase in cautery artifact or decreased quality of resections and feel this is an effective and safe method of TURBT performance and education.

En-Bloc Bladder Tumor Resection

Among the most prominent developing approach for endoscopic management of bladder tumors is en-bloc resection. Techniques for en-bloc resection of larger bladder tumors (>1 cm) have been introduced through a number of approaches with the supposition that removal of tumors in their entirety provides better orientation for pathologic diagnosis and, in theory, may limit tumor recurrences secondary to seeding by tumor fragments created in the process of standard resections [54–57]. A meta-analysis of seven trials (including just one randomized controlled trial) revealed outcomes favoring en-bloc TURBT in comparison to conventional endoscopic resection in hospitalization time, catheterization time, bladder perforation, and obturator nerve reflex without any increase in operative time. Perhaps most interesting, 24-month recurrence rate favored en-bloc resection (OR 0.66, 95% CI 0.47–0.92, $p = 0.02$) [55]. Further evaluation of en-bloc resection techniques will clarify outcomes in comparison to standard TURBT and identify appropriate candidates for application of these methods.

Conclusion

TURBT is an essential procedure in the evaluation and management of bladder cancer. Quality of resection through tumor eradication and adequate staging directly impacts patient outcomes including peri-procedural morbidity, oncologic efficacy, and costs. Though relatively unchanged for many years, recent advances in technology have improved the safety and efficacy of endoscopic bladder tumor resections. Further work will define optimal implementation of bipolar cautery and photodynamic aids as well as standardized resection techniques and education to maximize safety and patient benefits from endoscopic resection.

Compliance with Ethical Standards

Conflict of Interest Daniel Zainfeld and Siamak Daneshmand declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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