Diagnosis and Treatment of Bladder Endometriosis: State of the Art

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Abstract
Background: The bladder is the most common affected site in urinary tract endometriosis, being diagnosed during gynecologic follow-up. The surgical urological treatment might lead to good results. Study Objective: To define the state of the art in the diagnosis and treatment of bladder endometriosis. Methods: We performed a literature review by searching the MEDLINE database for articles published between 1996 and 2011, limiting the searches to the words: urinary tract endometriosis, bladder endometriosis, symptoms, diagnosis and treatment. Results: Deep pelvic endometriosis usually involves the urinary system, with the bladder being affected in 85% of cases. The diagnosis has to be considered as a step-by-step procedure. Currently, the treatment is usually surgical, consisting of either transurethral resection or partial cystectomy, and eventually associated with hormonal therapy. The hormonal therapy alone counteracts only the stimulus of endometriotic tissue proliferation, with no effects on the scarring caused by this tissue. The overall recurrence rate is about 30% for combined therapies and about 35% for the hormonal treatment alone. Conclusions: The bladder is the most common affected site in urinary tract endometriosis. Most of the time, this condition is diagnosed because of the complaint of urinary symptoms during gynecologic follow-up procedures for a deep pelvic endometriosis: a close collaboration between the gynecologist and the urologist is advisable, especially in highly specialized centers. The surgical urological treatment might lead to good results in terms of patients’ compliance and prognosis.

Introduction
Deep infiltrating pelvic endometriosis (DIE) is defined as implantation of the stroma and/or endometrial glandular epithelium outside the endometrial cavity and the uterine musculature, penetrating into the retroperitoneal space or the wall of the pelvic organs to a depth of at least 5 mm [1]. Locations of DIE include: the torus uteri, posterior fornix, uterosacral ligaments, rectum, vagina, and urinary tract [2].

The incidence of urinary tract endometriosis (UTE) has increased during the last few years and, nowadays, it ranges from 0.3 up to 12%, considering all women affected by endometriosis [2–10].
Most of the time, this condition is diagnosed because of the complaint of urinary symptoms during gynecologic follow-up procedures for DIE. Thus, a close collaboration between the gynecologist and the urologist is necessary in order to establish both the correct diagnostic procedure and the most adequate treatments.

Materials and Methods

We performed a literature review by searching the MEDLINE database using PubMed and Scopus for articles published between January 1996 and July 2011. Electronic searches were limited to the key words: urinary tract endometriosis, bladder endometriosis, symptoms, diagnosis, and treatment. We found a total of 132 articles about UTE and a total of 74 specifically related to bladder endometriosis (BE). Among these, 70 were original articles and 4 were reviews.

Results

Epidemiology and Definition

Within the urinary system, the bladder is the most commonly affected site (85% of cases). Nowadays, 350 cases have been described in the literature (fig. 1) [10]. In 36% of cases the endometriosis is localized only in the bladder. A detrusor nodule per se does not represent a risk factor for additional urologic lesions. However, different locations of UTE may coexist, especially bladder and ureters [9, 11–13].

BE usually affects women in the reproductive age group with an average age of 35 years [13]. Postmenopausal BE is extremely rare because endometriotic tissue is dependent upon estrogen for continued growth and generally undergoes regression after menopause [13–15]. Some authors have found that heritability might play a role in the development of BE in many patients [16, 17].

According to the onset type, BE is defined as ‘primary’ or ‘secondary’: (1) primary BE is a spontaneously occurring disease, diagnosed in 11% of overall patients diagnosed with DIE [18–27], while (2) secondary BE is defined as an iatrogenic lesion, occurring after pelvic surgery, such as cesarean delivery or hysterectomy [18–27]. Up to 50% of patients with BE have a history of past pelvic surgery [13].

BE lesion usually evolves from the serosal surface of the bladder toward mucosa and it is often multifocal, while the trigone and the dome are the most frequently affected sites [18–27].

Pathogenesis

Although the pathogenesis of BE is still being debated, four etiologic hypotheses are widely supported: the embryonal theory, the migratory or metastatic theory, the transplantation theory, and the iatrogenic theory.

Embryonal Theory

BE might originate from the Müllerian remnants, located especially in the vesicouterine/vesicovaginal septum [9, 20, 25]. Donnez et al. [25] were the first to propose this theory, but the histological evidence of Müllerian remnants in the urothelium of the bladder has been doubted by some authors [9].

Migratory or Metastatic Theory

This theory, supported by the findings of Vercellini et al. [19, 20, 22, 23], postulates that products of menstruation are regurgitated into the pelvis through the fallopian tubes in a retrograde fashion and then implant on the bladder wall. As a matter of fact, the bladder constitutes a privileged target for the implantation of regurgitated endometrial cells because it is located in the anterior cul-de-sac, a dependent portion of the peritoneal cavity. After implantation, regurgitated endometrial cells ‘sandwiched’ between the bladder dome and the anterior uterine wall trigger an inflammatory process of the peritoneum, leading to adhesion of the two organs [19, 20, 22, 23].

Subsequently, cryptomenstruations and the inflammatory response originate from a fibrotic nodule that is buried under the peritoneum, giving the false impression of a primary nodule of the vesicovaginal septum [26]. At surgery, detrusor nodules are almost invariably found ad-
herent to the uterine body, therefore cranial to the vesico-
vaginal and vesicocervical septum which by definition do
not extend beyond the uterine cervix. This is the most
commonly accepted theory [10, 11, 18–20, 25].

**Transplantation Theory**

An alternative mechanism of pathogenesis, mainly
supported by anatomopathological studies, postulates
that BE should be defined as bladder adenomyosis, origin-
ating as extension of adenomyotic lesions and transport
through via lymphogenous or hematogenous emboli-
zation, or by direct extension of adenomyotic nodules
through the uterine wall [25–27]. Nevertheless, imaging
and surgical findings demonstrate that, in the vast major-
ity of cases, BE originates intraperitoneally in the vesico-
uterine pouch and that the association with uterine ade-
nomyosis is not frequent [10, 11, 18, 19, 27].

**Iatrogenic Theory**

A different pathogenesis may be proposed for BE
which ensues after a cesarean section. In this case, the
vesical nodule does not represent only one site of a more
generalized disease, but it is usually isolated and may be
caused by intraoperative dissemination of endometrial
cells or by a suboptimal surgical technique for closure of
the low transverse uterine incision [7, 10, 18, 19, 25, 28–
31].

**Symptoms**

The symptoms caused by BE vary considerably and
depend on the location and size of the lesion [10, 32, 33].
Thirty percent of the patients with BE remain asymptom-
atic and the diagnosis is incidental, because of follow-up
procedures both for a known DIE and/or for infertility.
In most of these cases, the BE lesions have diameter of
1–2 cm. Nevertheless, 70% of women with BE present
with urinary storage symptoms at time of first diagnosis.
In these cases, the lesions affect the detrusor, especially
in the trigone and dome [10]. As a matter of fact, the con-
dition basically manifests as an acute urethral syndrome
with frequency, tenesmus, burning sensation, pain dur-
ing micturition, dysuria, and suprapubic discomfort and
pain [7, 10, 11, 17, 32–35].

Hematuria seems to be a less frequent symptom, be-
ing described by 20–35% of patients. This is due to the
fact that BE rarely infiltrates and ulcerates the mucosal
layer of hollow viscera [10, 32, 36, 37]. Menouria (i.e. he-
maturia coinciding with menstruation) is not as com-
mon as acute urethral syndrome, appearing in only 20–
25% of cases when the mucosa is affected [35]. Moreover,
40% of patients affected by BE have reported these
symptoms occurring in a cyclic manner, with predomi-
nance during the premenstrual period [10, 19, 35, 36].
These are overlapping symptoms with many different
urological conditions, such as recurrent cystitis-overac-
tive bladder, bladder carcinoma, interstitial cystitis and
chronic urethral syndrome [31, 33, 35, 37–43]. Moreover,
malignant transformation arising from infiltrative
BE in the form of endometrioid adenocarcinoma or ad-
enosarcoma has been occasionally reported in the lit-
erature [39, 43].

**Diagnosis**

The diagnosis has to be considered as a step-by-step
procedure.

**Physical Examination**

The physical examination (bimanual per vaginam ex-
amination) is considered positive and therefore sugges-
tive of endometriotic infiltration of the pelvis if there is:
a palpable nodule, or thickened area, or a palpable cystic
expansion with topographic-anatomical correlation to
uterosacral ligaments, vagina, rectovaginal space, pouch
of Douglas, the rectosigmoid and the posterior wall of the
urinary bladder (posterior wall) [9, 44, 45]. Moreover, the
presence of lesions in these areas might suggest the in-
volvement of the ureter, with or without consequent dif-
f erent grades of hydronephrosis, up to silent renal func-
tion loss [11, 45].

**Serux Examinations**

All patients should be assessed for anemia. As a mat-
ter of fact, extended BE might lead to significant ane-
mization. All patients should also be assessed for renal
function by blood creatinine measurements. As men-
tioned above, a silent loss of renal function is not so rare
[11, 45].

**Urine Examinations**

The urine should be evaluated for evidence of micro-
scopic or macroscopic hematuria and cultured to rule out
an infectious etiology for irritative voiding symptoms.
Urine cultures are usually negative. Moreover, urine cy-
tology is mandatory because of the necessity of differen-
tial diagnosis for irritative voiding symptoms in order to
exclude bladder cancer [33, 35].
Ultrasound

Ultrasound (US) is the first step in diagnosis of BE. This is mainly due to low cost, ready availability, and lack of radiation exposure. Combination of abdominal, transvaginal (TV) and transrectal US, depending on the complaints, may reveal endometriosis in infrequent sites, including bladder [18, 45–49].

The TV approach is performed using a 5- to 9-MHz transducer for visualization of the bladder, both adnexa, the uterus, the vagina and rectovaginal space, the uterosacral ligaments and the rectosigmoid. The transducer has to be first introduced into the posterior vaginal fornix and withdrawn backwards to assess the pouch of Douglas, uterosacral ligaments, bladder and the vagina, in order to achieve adequate visualization of all these structures [45, 48, 50, 51].

Performed with the bladder full of anechoic urine, it allows a clear visualization of a heterogeneous, hyperechoic, intraluminal, usually spherical or comma-shaped vegetation, sometimes with small transonic formations, which protrudes from the posterior vesical wall or the vesical dome, with regular borders. Such nodules display few blood vessels at power Doppler [48, 50, 51].

A moderate amount of urine, creating an anechoic acoustic window, could facilitate the detection of nodules along the bladder wall, but excessive distension of the bladder pushes the dome away from the tip of the vaginal probe and this may make it more difficult to detect a nodule in the dome of the bladder. A plane between the detrusor nodule and the anterior uterine wall is generally clearly detected, excluding a leiomyoma. At median longitudinal scans, the lesions are usually supraisthmic [50, 51]. The maximum lesion diameter varies between 1 and 5 cm. The uterine body is invariably anteflexed.

As reported by different authors, the specificity and positive and negative predictive values of TV US for BE are about 100%. The sensitivity is under 50% because the detection rate is strongly related to mean lesion diameter as finally measured by the pathologist (≈3 cm) and to a history of previous surgery for endometriosis. Grasso et al. [51] have evaluated the sensitivity and specificity of three-dimensional TV US for the diagnosis of DIE. Similar to conventional TV US, specificity is about 100% and sensitivity still remains low, i.e. about 25%.

Pelvic Magnetic Resonance

Pelvic magnetic resonance (MR) reaches sensitivity up to 88% and specificity up to 99% for the diagnosis of BE; the diagnostic accuracy is about 98%. These considerations justified the employment of MR as a complementary examination in complex cases of endometriosis with extensive adhesions and as gold standard for the diagnosis of BE [48, 50–54].

In clinical practice, a conventional MR protocol for evaluating pelvic endometriosis includes sagittal and axial $T_2$- and $T_1$-weighted MR images before and after fat suppression. Bladder endometriomas are characterized by high signal intensity on $T_1$-weighted images and low signal intensity on $T_2$-weighted images. The MR sequences taken in the coronal plane are of particular interest as they allow an accurate investigation of associated lesions in the pelvis, which have been documented in 50–70% of cases.

Pelvic MRI performed with a 3-Tesla system guarantees high spatial and contrast resolution, providing accurate information about endometriosis implants, with a good pre-surgery mapping of the lesions involving both bowels and bladder surface and rectouterine ligaments. Few data are available about the contribution of intravenous gadolinium, rectal or vaginal administration in the diagnosis of deep endometriosis (table 1) [48–54].

Cystoscopy

The cystoscopy still represents one of the most cost-effective tests. Due to the intraperitoneal origin of the lesion, cystoscopic findings may be normal. Nevertheless, cystoscopy may demonstrate an intraluminal mass of the posterior bladder wall or dome.

The morphology of BE lesions might change with the phases of menstrual cycle, with the best characterization obtained before and during menstruation. As a matter of fact, during menstruations, the endometriotic nodules are larger and more congested, and the cystoscopic visualization is clearer. Small lesions affecting only the bladder adventitia may not be visible by cystoscopy.

BE lesions often appear as an adenomatous and irregular nodular mass, with different shapes and colors: the blue-red, blue-black, or blue-brown lesions are the more common findings. The urothelium is not usually ulcerated [5, 7, 13, 16, 17, 35, 44, 55]. Moreover, they might be isolated or multifocal, approximately 1–3 cm in diameter and usually located at the dome or at the base. Calculating the distance between the ureteral orifices and the lower endometriotic margin is crucially important in order to define the most correct surgical approach. In patients not operated previously, the distance between the caudal border of the endometriotic lesion and the interureteric ridge is rarely <2 cm.

Endoscopic biopsy is critical to exclude bladder carcinoma, varices, papillomas or angiomas as well as detrusor mesenchymal tumors. However, with the exception of...
transurethral resection (TUR) procedures, biopsy at cystoscopy is not always diagnostic for endometriosis. In those rare cases in which, at cystoscopic evaluation, the caudal border of the endometriotic lesion is <2 cm away from the interureteric ridge, a ureteroneocystostomy might be required, and the surgical procedure must be planned accordingly. A close proximity of endometriotic nodule with the vesical trigone is more frequent among patients who have already undergone transurethral resectoscopic surgery [56].

**Differential Diagnosis**

When the bladder mass or lesion has been documented by imaging techniques and/or cystoscopy, the differential diagnosis should include bladder carcinoma, angiomas, leiomyoma, amyloidosis, malakoplakia, glandular cystitis, nephrogenic adenoma and extravesical processes such as diverticulitis with histologic study necessary in almost all cases.

**Treatment**

The treatment of UTE is controversial because the rarity of this condition makes randomized studies almost unfeasible. Specifically, the treatment of BE may depend on several factors, such as age, fertility preferences, extent of disease, severity of lower urinary tract symptoms, presence of other pelvic lesions, and degree of menstrual dysfunction [5, 7, 11, 13]. The treatment might be medical or surgical, or a combination.

**Medical Treatment**

The aim of most medical (or hormonal) treatment (HT) is to raise a regression of the endometrial tissue [35, 57–66]. The most common therapies used in the treatment of endometriosis include: gonadotrophin-releasing hormone (GnRH) agonists and antagonist, progestins and combined oral contraceptives (table 2). HT can induce temporary regression of DIE and may often serve as the initial treatment for younger women and those desiring to preserve fertility [13].

In this context, local progestogens such as an IUD with levonorgestrel may be useful as a conservative medical approach. Although this treatment is normally used in gynecology as a contraceptive or for idiopathic menorrhagia, it is effective in endometriosis foci in the pelvis and vesicovaginal septum possibly because it provides high concentrations of drug to the endometrium and adjacent areas despite low plasma concentrations. This of-

<table>
<thead>
<tr>
<th>Table 1. Role of MR in the diagnosis of BE in the context of DIE</th>
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<tr>
<td><strong>Reference (first author)</strong></td>
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<tr>
<td><strong>Key points</strong></td>
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<tr>
<td>Manganaro 2011 [52]</td>
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<td>Bazot 2011 [53]</td>
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<td>Busard 2010 [54]</td>
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<td>Chamié 2011 [50]</td>
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</table>
fers two important advantages: it is effective for 5 years and it does not affect future fertility after the treatment is discontinued.

Even if all these drugs may alleviate the severity of pelvic pain, dysmenorrhea and dyspareunia, the symptoms often recur when therapy is discontinued [5]. Moreover, they are frequently associated with suboptimal safety and tolerability and they always postpone child wish without improving fertility.

Finally, the relapse rate in DIE is quite high (about 56%), revealing that such treatment only induces a temporary disappearance of the lesions in patients with deep endometriosis and BE, too. All these features strictly impact on long-term use and compliance.

The ideal targets for HT, especially GH-RH analogs, are bladder lesions with a diameter < 5 mm, in postmenopausal women. Westney et al. [35] reported partial or complete resolution of symptoms in 12 of their 14 patients at a mean follow-up of 18.6 months. Close follow-up is recommended.

As a matter of fact, medical management appears to have a high recurrence rate after treatment cessation, and is often considered a palliative modality for the treatment of BE. Additionally, some authors have noted that bladder pain and the desmoplastic reaction within the detrusor from repetitive bleeding and resorption of menstrual debris might be poorly responsive to hormonal manipulation.

### Surgical Treatment

The surgical treatment for BE includes different surgical approaches (table 3). An accurate preoperative workup (questioning, clinical examination and imaging information) is essential for planning a correct surgical approach. Moreover, it is fundamental: (1) to rule out vesical epithelial malignancy, (2) to ascertain the precise location of BE nodule (distance with the ureteral meatus and the lower endometriotic margin), and (3) to define the ureteral status. This leads to specify the surgical procedures required in order to achieve complete excision of symp-

### Table 2. Medical treatment of BE

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Side effects</th>
<th>Reference (first author)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined oral contraceptives</td>
<td>All different types of combined oral contraceptives</td>
<td>These drugs bring about a so-called ‘pseudopregnancy regimen’. The goal of treatment is suppression of menses, leading to therapeutic amenorrhea.</td>
<td>Breakthrough bleeding, nausea, headache, elevated risk of venous thromboembolism, loss of libido, cutaneous reaction, sodium fluid retention.</td>
<td>Vercellini, 2011 [73] de Ziegler, 2010 [74] Hansen, 2010 [75] Takamura, 2009 [76]</td>
</tr>
</tbody>
</table>

### Table 3. Type of surgical approach for BE

- TUR
- Partial cystectomy
- Laparotomy with or without associated cystoscopy
- Combined transurethral partial cystectomy and laparoscopic reconstruction of bladder
- Robotic approach
- Association of surgical and medical therapy

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tomatic DIE lesions, that represents the only way to prevent the recurrence [77–81]. As a matter of fact, recurrence corresponds to actual persistence of BE lesions that were left in place as the result of an incomplete initial surgical removal [10, 77, 79].

Fedele et al. [89] have shown that the greatest risk factor for recurrence after surgical management of BE was the patient’s age. The younger the patient, the greater the risk of recurrence because surgeons are likely to be more hesitant in carrying out radical treatment with partial cystectomy [81]. Moreover, complete excision results in significant reduction of pain and improvement in the quality of life [60, 63, 65–68] (table 4).

**Partial Cystectomy.** Partial cystectomy is a bladder-preserving management procedure that involves full-thickness surgical excision of the BE and surrounding bladder wall. Generally, segmental bladder resection for detrusor endometriosis is a relatively simple and safe procedure. Several reports demonstrated the excellent surgical outcomes of this approach in terms of symptom relief and recurrence rate, whether the procedure is carried out at laparotomy or laparoscopy [2, 10, 70, 72–74]. Concomitant cystoscopy can be useful for better defining the margins of the endometriotic lesion to be resected. Moreover, according to the surgeon’s preference, preventive cystoscopic catheterizations of the ureters may be advisable, especially when the distance between the caudal border of the endometriotic lesion and the interureteric ridge is <2 cm [72, 75–77] (table 4).

Laparoscopic Partial Cystectomy: The laparoscopic approach includes the dissection of the vesicouterine space in order to mobilize the nodule and dissect the bladder with excision of the whole nodule together with any adhesions involving the anterior uterine wall and the vesicouterine fold peritoneum. As it is usually not possible to remove the detrusor nodule without opening the bladder lumen, an intentional perinodular incision through the vesical dome is suggested by different groups [56]. The most favorable anatomical situation is when the endometriotic lesion affects the bladder dome. A more complex anatomical situation is encountered when the endometriotic lesion is located on the posterior wall of the bladder. In these cases, segmental bladder resection might be performed by lysis of any adhesions between the anterior uterine wall and the vesicouterine fold of peritoneum. Very often, one or both round ligaments are distorted and involved in the adhesive process. The lesion is excised with mechanical scissors or unipolar electricity, and the bladder is finally oversewn with two transverse watertight fine synthetic absorbable sutures [5, 13, 82] (table 4).

| Table 4. Criteria for choosing surgical approach in the treatment of bladder endometriosis
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<tr>
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<tbody>
<tr>
<td>TUR</td>
<td>Partial cystectomy (PC)</td>
<td>Combined TUR and laparoscopic PC</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>no</td>
<td>open</td>
<td>laparoscopic</td>
</tr>
<tr>
<td>Premenopausal women</td>
<td>Rate of recurrence about 20–30%, indeed inversely related to the patient’s age</td>
<td>Normal bladder function</td>
<td>Bladder lesion located far from bladder neck, ureteral meatus and trigone</td>
</tr>
<tr>
<td>Pregnancy desire</td>
<td>Necessity of perforating the bladder wall because of radicality of resection</td>
<td>Normal bladder capacity</td>
<td>Free margins of 1–2 cm</td>
</tr>
<tr>
<td>First diagnosis of bladder lesion and necessity of histopathological examination</td>
<td>First diagnosis of bladder lesion</td>
<td>Monofocality</td>
<td>Precise preoperative definition of the lesion</td>
</tr>
<tr>
<td>Women who approach menopause</td>
<td>Free margins of 1–2 cm</td>
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some healthy tissue. The bladder suture is generally performed by means of a single layer. A cystoscopy at the end of the procedure is advisable in order to ensure watertight closure and to check the ureteral orifices integrity. The outcome is excellent in different series, with pain relief reported in 95–100% of patients. Laparoscopy also permits simultaneous treatment of extravesical lesions and concomitant castration with or without hysterectomy (that is the preferable approach for patients without pregnancy desire or women approaching menopause). Finally, laparoscopic partial cystectomy offers the same results as open surgery with several advantages, including less bleeding, shortened operative time, shortened hospital stay, quicker return to work, a major reduction in postoperative morbidity [75–82] (table 4). Combined transurethral partial cystectomy and laparoscopic reconstruction of bladder for the management of BE and coexisting abdominal endometriosis fits into the trend for minimally invasive surgery and it might be considered as an alternative treatment to traditional laparotomy in women with BE, especially in those who have simultaneous pelvic endometriosis. This approach requires a combined surgical treatment by a gynecologist and urologist or an experienced laparoscopic urologist [87, 88] (table 4).

Robotic Approach: Compared with standard laparoscopy, robot-assisted laparoscopy has the advantage of an improved level of freedom of instrumentation that might allow for an improved suturing technique. However, the longer set-up time and greater expense limits its use only in reference centers. Few case reports are described in the literature [91–94].

Conclusions

Bladder involvement is frequently documented in the context of DIE; it rarely represents the only manifestation of endometriosis. BE is commonly associated with severe urinary symptoms. Both adequate diagnosis and successful treatment should be completed at reference centers where a close collaboration between a dedicated gynecologist and urologist is available. HT still remains an option in a subset of patients, while surgical treatment leads to satisfactory long-term outcome results in terms of patient compliance and prognosis.

References


