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TESI DI LAUREA

Perioperative, Oncological and Functional Outcomes of Robot-Assisted Radical Cystectomy with Totally Intracorporeal Neobladder using the Ves.Pa. (Vesica Patavina) Technique

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ABSTRACT

Background: For patients with Muscle Invasive Bladder Cancer (MIBC), radical cystectomy constitutes the main surgical treatment. Implementing a Robot-Assisted Radical Cystectomy (RARC) offers distinct advantages in terms of the patients' perioperative course and functional outcomes. While the construction of a Totally Intracorporeal Neobladder represents the most critical phase of the surgery, the Ves.Pa. (Vesica Patavina) technique has become an established reconstructive procedure.

Objective: To evaluate the perioperative, oncological and functional outcomes of the Ves.Pa. technique for the construction of a Totally Intracorporeal Neobladder after RARC.

Materials and Methods: A prospective study was conducted on male and female patients who underwent RARC and reconstruction with Ves.Pa. Neobladder. All procedures were performed by experienced surgeons in a tertiary referral centre. The participants included patients treated for Muscle Invasive Bladder Cancer and Non-Muscle Invasive Bladder Cancer in selected cases. The surgical procedure was Robot-Assisted Radical Cystectomy with Totally Intracorporeal Neobladder using the Ves.Pa. technique. Postoperative and functional outcomes were assessed using the Clavien-Dindo classification and the IPSS and ICIQ-UI SF questionnaires, respectively.

Results: A total of 100 patients were treated. The median operative time was 400 min, and the median estimated blood loss was 400 ml. The incidence of high-grade complications was remarkably low, with 6% of the patients experiencing early grade-3 complications and 7% of the patients experiencing late grade-3 complications. The mortality was 0% in the first 90 POD. All patients had clear surgical margins. Recurrence-free survival was 90% at the 12-month follow-up and 84% at the 36-month follow-up. At a median follow-up of 11 months, 53% of the patients had moderate urinary symptoms, and 42% of the patients had moderate urinary incontinence. 21% of the patients were

fully continent, while severe urinary incontinence was experienced by approximately 25% of the patients. The median number of pads used was 0 during the day and 1 during the night.

Conclusions: RARC with Ves.Pa. intracorporeal neobladder offers promising results for the treatment of patients with bladder cancer. Perioperative outcomes, especially for high-grade complications and mortality, are in agreement with or superior to the best available literature. Furthermore, the technique demonstrates favourable oncological outcomes in terms of recurrence-free survival. Functional outcomes are ultimately acceptable and in agreement with other studies about different neobladder techniques.

1. BACKGROUND: BLADDER CANCER

1.1 EPIDEMIOLOGY

According to the Global Cancer Observatory[1], incidence and mortality of bladder cancer respectively reach the ninth and the thirteenth position worldwide and in both sexes. In 2022, the total number of new cases was 614,298, and the total number of deaths was 220,596.

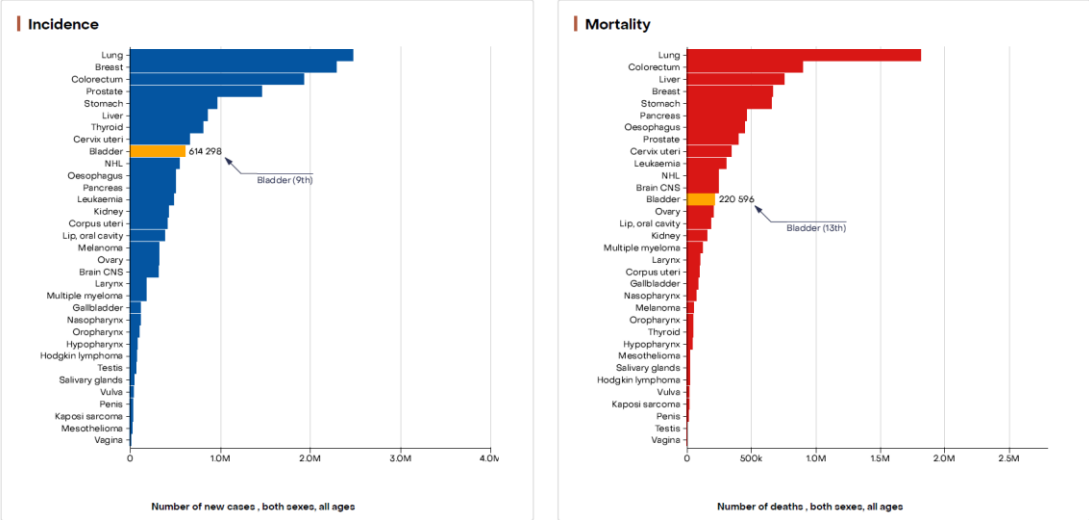

Figure 1. Incidence and mortality of bladder cancer worldwide.

Amongst males, bladder cancer's incidence rises to the sixth position, with 471,293 new cases in 2022 (76.7% of the total number of new cases of bladder cancer worldwide), and its mortality rises to the ninth position, with 165,672 deaths in 2022 (75.1% of the total number of deaths from bladder cancer worldwide).

The worldwide age-standardized incidence rate (per 100,000 people per year) is 5.6 for both sexes, 9.3 for males and 2.4 for females. The worldwide age-standardized mortality rate (per 100,000 people per year) is 1.8 for both sexes, 3.1 for males and 0.8 for females.

Europe is the continent with the highest rate of incidence (224,777 new cases in 2022 or 36.6% of the total number of new cases of bladder cancer in 2022); however, Asia is the continent with the highest mortality rate (92,510 deaths in 2022 or 41.9% of the total number of deaths for bladder cancer in 2022), while Europe has the second highest mortality rate, with 70,383 deaths in 2022 or 31.9% of the total number of deaths from bladder cancer in 2022.

In Europe, the age-standardized incidence rate (per 100,000 people per year) is 12 for both sexes, 21.1 for males and 5 for females, while the age-standardized mortality rate (per 100,000 people per year) is 3 for both sexes, 5.4 for males and 1.2 for females.

In Italy, incidence and mortality of bladder cancer respectively reach the fifth and the seventh position in both sexes, and the fourth and the fifth position in males. In 2022, the total number of new cases was 34,580 (7.9% of the total number of new cases of cancer), and the total number of deaths was 8,254 (4.3% of the total number of deaths from cancer). Amongst males, the number of new cases in 2022 was 27,211 (11.7% of the new cases of cancer in the male sex), and the number of deaths in 2022 was 6,373 (6.1% of the deaths from cancer in the male sex).

In Italy, the age-standardized incidence rate (per 100,000 people per year) is 18.1 for both sexes, 30.4 for males and 7.7 for females, while the age-standardized mortality rate (per 100,000 people per year) is 3.1 for both sexes, 5.5 for males and 1.2 for females.

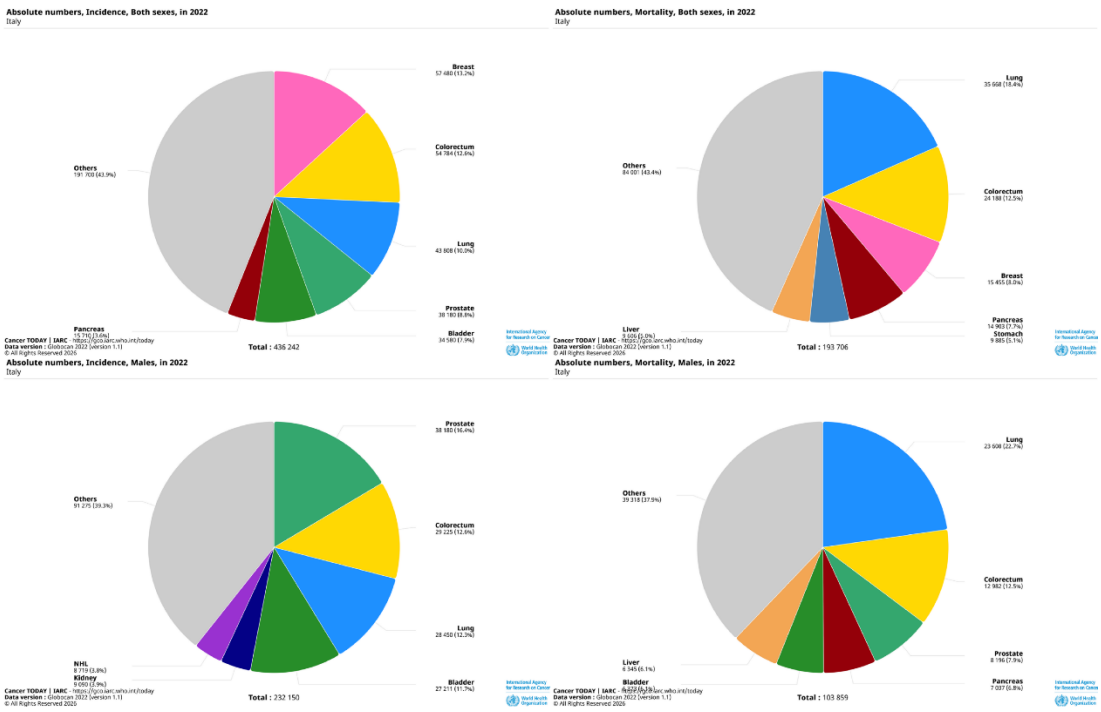

Figure 2. Incidence and mortality of bladder cancer in Italy in 2022, in both sexes and in males.

1.2 RISK FACTORS

Bladder cancer is a disease with a complex and multifactorial aetiology, hence many risk factors can facilitate its development. The most important ones will be presented in the following paragraphs.

1.2.1 TOBACCO SMOKING

It has been proved that exposure to tobacco and bladder cancer are linked by a causal relationship.[2] It is estimated that cigarette smokers' risk of developing bladder cancer is 3 times higher than in the general population[3], and that almost half of the cases of bladder cancer are caused by tobacco smoking.[4] For this reason, it is recognized as the most important modifiable risk factor for bladder cancer.

Tobacco smoking can drive the carcinogenesis of urothelial bladder cancer because cigarettes contain aromatic amines and polycyclic aromatic hydrocarbons; these substances are metabolized and excreted through the kidneys and the urinary tract, and their contact with the urothelium, which is longer in the bladder, can damage the DNA of the cells, starting the carcinogenic process.

In former smokers, the factor which impacts most on the development of bladder cancer is the duration of smoking habit. Nonetheless, the risk of developing bladder cancer decreases almost immediately after giving up smoking: in particular, in the first 4 years after quitting smoking, a decrease of 40% has been observed, and after 25 years the detected reduction is of 60%.[5] However, the risk of bladder cancer remains 2-folds higher in former smokers than in non-smokers.[3] Otherwise, there is no evidence about the impact of quitting smoking when bladder cancer has yet developed.[6] In any case, it is strongly recommended to counsel patients to stop active and passive smoking.[7]

1.2.2 OTHER RISK FACTORS

Even though tobacco smoking is the most important risk factor indeed, bladder cancer can have other aetiologies.

First of all, the occupational exposure to aromatic amines (such as benzidine, 4-aminobiphenyl, 2-naphthylamine and 4-chloro-o-toluidine), polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons causes up to 20% of urothelial bladder cancers.[8] These compounds can be found in dyes, varnishes and other petroleum derivates. It is necessary to underline that it is not easy to recognize bladder cancer as an occupational disease as it develops with a delay of approximately 30 years from the exposure.[9]

Furthermore, bladder cancer can establish itself in a tissue that had been exposed to external-beam radiotherapy (ESRT) for other malignancies of the

pelvis.[10] When it appears with a latency of at least 10 years from radiotherapy, it is considered a radio-induced tumour.

In addition, it has been proved that cyclophosphamide[4], an alkylating agent used for chemotherapy mainly in haematological malignancies, can facilitate the development of bladder cancer.

Another risk factor for the development of bladder cancer is chronic inflammation of the bladder[7], which can be caused by different factors, such as: schistosomiasis, a parasitic infection from *Schistosoma haematobium*, which is frequent in Northern Africa and leads to the development of squamous bladder cancer; urinary calculi and permanent urinary catheterization.

Finally, some studies have identified female sex as a factor that contributes to a poorer prognosis after radical cystectomy[11] and in the two first years after diagnosis. The prognostic gap between men and women could not be due to a different biology of the tumour but to a delay in the diagnosis in female patients, for whom cystitis represents an important confounding factor in differential diagnosis because of its high frequency.[12]

1.3 DIAGNOSTIC EVALUATION

1.3.1 ANAMNESIS AND COMORBIDITIES

The first approach to the patient should include a general evaluation about their health status, hence it conditions the therapeutic pathway. The urologist should know about the remote and recent pathological anamnesis, both medical and surgical, as it heavily influences the outcome of a radical cystectomy.

Moreover, calculating scores could be useful to evaluate in an objective way the patient as a whole, not limiting to their disease only. In particular, the Eastern Cooperative Oncology Group Scale of Performance Status (ECOG PS) evaluates the impact of cancer disease on the functionality of the patients

with a number from 0 to 5[13], whilst the Charlson Comorbidity Index[14] considers the patients' comorbidities and relates them to their mortality rates.

ECOG Performance Status Scale	
0	Fully active, without restriction
1	Restricted in physically strenuous activity, able to carry out light work
2	Capable of all selfcare but unable to carry out any work activities; >50% of waking hours
3	Confined to bed or chair >50% of waking hours
4	Completely disabled; totally confined to bed or chair
5	Dead

Table I. ECOG Performance Status Scale.[13]

Charlson Comorbidity Index	
1 point	Myocardial infarction Congestive heart failure Peripheral vascular disease Cerebro-vascular accident or TIA Dementia Chronic Obstructive Pulmonary Disease (COPD) Connective tissue disease Peptic ulcer disease Mild liver disease Uncomplicated diabetes mellitus Age between 50-59 years-old
2 points	Complicated diabetes mellitus Hemiplegia Moderate to severe kidney disease History of other tumours Leukaemia Lymphoma Age between 60-69 years-old

3 points	Moderate to severe liver disease Age between 70-79 years-old
4 points	Age between 80-89 years-old
5 points	Age ≥ 90 years-old
6 points	Solid tumour metastasis AIDS

Table II. Charlson Comorbidity Index.[14]

1.3.2 CANCER PRESENTATION AND DIAGNOSIS

In up to 50% of the cases, bladder cancer's first manifestation is haematuria, which can be visible (more common) or non-visible (found incidentally in urine examination). Other possible symptoms are irritating voiding symptoms (that could be wrongly diagnosed as recurrent cystitis), flank pain and bladder outlet obstruction. Rarely, does the disease present directly with metastasis-related symptoms.

1.3.2.1 URINARY CYTOLOGY

Diagnostic workup includes urinary cytology as a first insight on the presence of high grade urothelial cancer (HGUC) and other specimens based on the 'Paris System' diagnostic categories[15], which are the following:

- adequacy of urine specimens (Adequacy);
- negative for high-grade UC (Negative);
- atypical urothelial cells (AUC);
- suspicious for high-grade UC (SHGUC);
- high-grade UC (HGUC).

Urinary cytology can analyze voided urine, thus evaluating the entire urinary tract of the patient, or bladder lavage, thereby evaluating bladder cells only; it

is performed on three specimens and it has a low sensitivity (especially for non-HGUC) and a high specificity for HGUC (up to 90%) and CIS.

However, it is challenging to evaluate the specimen in an objective way, especially if the pathologist is not very experienced or if there are confounding factors such as degenerative artifacts, sparse cellularity, or reactive atypia: for this reason, bladder cancer is not ruled out if cytology is negative.[16]

1.3.2.2 IMAGING

The first radiological approach when bladder cancer is suspected is to require an ultrasound of the inferior abdomen, which should visualize the kidneys, the ureters and the bladder.[17] The advantages of this exam are its high specificity, low cost and that it is non-invasive. Its disadvantages are that it cannot visualize flat lesions and that it is not adequate for the study of the upper urinary tract.

CT urography is the gold standard for the evaluation of the local spread of the tumour, but normally it is used for the staging, after the definitive histological diagnosis.

1.3.2.3 CYSTOSCOPY

When the urinary cytology or the ultrasound are positive for bladder cancer, the next step is to visualize the tumour with an outpatient flexible cystoscopy, which aims to display the mucosa of the bladder walls entirely and to map the lesions.[17]

White light cystoscopy (WLC) is the traditional technique for diagnosis and surveillance; even though it is useful for exophytic lesions, it has low sensitivity for flat lesions and CIS (carcinoma in situ) and its detection rates vary between 62% and 84%. For this reason, other techniques have been developed and introduced in clinical practice, such as photodynamic diagnosis (PDD), which

uses 5-aminolevulinic acid or hexaminolevulinate as photosensitizers, and narrow-band imaging (NBI). A metanalysis by Choi et al.[18] found that both NBI and PDD show a higher sensitivity, with PDD showing the highest sensitivity for the detection of CIS, while WLC still showed the highest specificity.

In selected cases, if the patient has already undergone other imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound (US), that visualized the cancer unequivocally, it is possible to defer cystoscopy.

1.3.2.4 TRANS-URETHRAL RESECTION OF THE BLADDER (TURB)

Finally, in order to obtain diagnostic specimens, a trans-urethral resection of the bladder (TURB) has to be performed with a rigid cystoscopy and under anaesthesia. When an exophytic lesions is present, the exophytic part should be resected first, followed by the bladder wall, and the two specimens should be sent to the pathologist separately.[7]

At least one specimen should include detrusor muscle; if not, the first TURB is considered incomplete and a revision TURB should be performed. The examination of the specimens by the pathologist constitutes the first diagnosis of bladder cancer and an initial staging of the primary tumour. If the tumor invades the detrusor muscle, bladder cancer is considered muscle-invasive (at least a T2 stage), but the final diagnosis has to be done after surgery, because it is not possible to distinguish T2a, T2b, or even T3 stage from the TURB specimen.[19]

If the patient had not undergone a flexible cystoscopy before, the bladder wall should be visualized entirely during TURB procedure.

If the urologist who is performing TURB individuates a suspicious area in the prostatic urethra, they should biopsy it too, even though a preoperative positivity of the urothelium of the prostatic urethra is not definitive. In fact, the

final response is given during the surgery, when the pathologist analyses a frozen section of the urethra. The confirmation of a urethral localization of the tumour constitutes a contraindication to orthotopic urinary derivations after radical cystectomy.

1.3.3 HISTOLOGY AND GRADING

According to the fifth edition of the WHO classification of urinary tract tumours, bladder cancer can present with the following histological subtypes:[20]

- Urothelial carcinoma (UC), which constitutes up to 90% of the cases:
  - Conventional or usual UC: pure UC with no divergent differentiation or subtype morphology;
  - UC with divergent differentiation: squamous (30-40%), glandular (up to 18%), trophoblastic, Müllerian (clear cell adenocarcinoma);
- UC subtype: micropapillary, nested, tubular and microcystic, large nested, lymphoepithelioma-like, small cell carcinoma, plasmacytoid, sarcomatoid, lipid-rich, clear cell, giant cell, poorly differentiated, mesenchymal.

It is important to consider that the urothelium is a tissue that can be found along the entire urinary tract, hence urothelial carcinoma can develop not only in the bladder but also in the ureters (upper urinary cancer).

The presence of divergent differentiations of urothelial carcinoma has been observed more frequently when the tumour is locally advanced; however, the most common differentiations, which are the squamous and glandular ones, are not associated with poorer prognosis.

On the contrary, some UC subtypes, for example micropapillary, plasmacytoid, sarcomatoid and small cell carcinoma, are associated with aggressive behaviour, high metastatic potential and, consequently, poorer prognosis.

In addition to the histology of the neoplasm, the pathologist also has to evaluate the grading of the specimen.[20] Two grading systems have been developed by WHO: in 1973, they developed a numeric system with grading from 1 to 3; in 2004, they developed a binary system, which included low grade (LG) tumours and high grade (HG) tumours.

The binary system, which is still used nowadays, defines low-grade lesions as UC presenting mild cytoarchitectural atypia, including grade 1 tumours and grade 2 tumours with relatively less atypia from the 1973 system; moreover, high-grade lesions show severe cytoarchitectural atypia, corresponding to grade 3 tumours and grade 2 tumours with more atypia from the 1973 system.

Finally, if the specimen shows papillary fibrovascular structures lined by thickened urothelium that lacks discernible cytological atypia it is classified as papillary urothelial neoplasm of low malignant potential (PUNLMP). Even though it does not differ much from low-grade lesions, the fifth edition of the WHO classification confirms its existence as a separate entity.

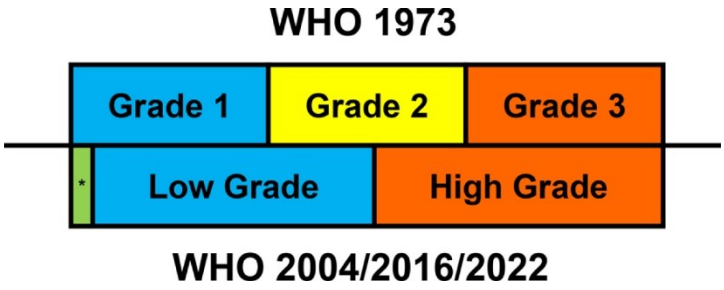

*Figure 3. Correspondence between ternary grading system (WHO 1973) and binary grading system (WHO 2004).[20] *PUNLMP*

1.4 STAGING AND CLASSIFICATION

For bladder cancer, the Tumour Nodes Metastasis (TNM) Classification should be used in order to stage the disease.[21]

1.4.1 CLASSIFICATION OF URINARY BLADDER CANCER

Primary Tumour (T):

- TX: Primary tumour cannot be assessed;
- T0: No evidence of primary tumour;
- Ta: Non-invasive papillary carcinoma;
- Tis: Carcinoma in situ (‘flat tumour’);
- T1: Tumour invades subepithelial connective tissue;
- T2: Tumour invades muscularis propria:
  - T2a: Tumour invades superficial muscularis propria (inner half);
  - T2b: Tumour invades deep muscularis propria (outer half);
- T3: Tumour invades perivesical tissue:
  - T3a: microscopically;
  - T3b: macroscopically (extravesical mass);
- T4: Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall or abdominal wall:
  - T4a: Tumour invades prostate stroma, seminal vesicles, uterus or vagina;
  - T4b: Tumour invades pelvic wall or abdominal wall.

Regional Lymph Nodes (N):

- NX: Regional lymph nodes cannot be assessed;
- N0: No regional lymph node metastasis;
- N1: Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac or presacral);
- N2: Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac or presacral);
- N3: Metastasis in a common iliac lymph node(s).

Distant Metastasis (M):

- M0: No distant metastasis;

- M1a: Non-regional lymph nodes;
- M1b: Other distant metastasis.

Non-Muscle Invasive Bladder Cancer (NMIBC) refers to Ta, Tis and T1 stages, and comprises 75% of all bladder neoplasms; it can be classified as PUNLMP, LG or HG. When the tumour invades the muscular layer of the bladder (T2, T3, T4) it is considered a Muscle Invasive Bladder Cancer (MIBC), which is diagnosed in 1 case of bladder cancer out of 4 (25%); it is always HG.

1.4.2 PROGNOSTIC EVALUATION OF MIBC

NMIBC and MIBC differ not only for the treatment but also for their prognostic evaluation, thus their differential diagnosis is essential. In particular, MIBC has a poor prognosis: after radical cystectomy, it has a life expectancy at 5 years of 58%, but it drops to 18% when lymph node invasion is detected by the pathologist.[22] Other factors that impact negatively on the prognosis of the patient are the staging of the disease (a higher T stage is associated with poorer prognosis), the detection of lymphovascular invasion and the positivity of surgical margins. Moreover, MIBC has an elevated metastatic potential with a higher risk of hepatic, pulmonary and bone metastasis.

For this reason, it is fundamental to perform a local and a distant staging of the disease.

1.4.3 LOCAL AND DISTANT STAGING

The gold standard for the distinction of T1 and T2 stages still remains the TURB with the pathological analysis of the specimen. The possibility to use MRI and VI-RADS (Vesical Imaging Reporting And Data System) score has been studied but it is not ready to become the standard of care.[23]

Then, the patient should undergo a contrast-enhanced computed tomography (CT) of thorax and abdomen to evaluate different aspects of the staging:

1. CT imaging of the pelvis (local staging) is useful to determine extravesical tumour extension for stages T3b and T4a and to evaluate invasion of lymph nodes of the pelvis. However, CT is not able to detect microscopic or small volume tumour localizations.[24]

2. CT urography (local staging) permits the visualization of the upper urinary tract and the evaluation of the presence of upper urinary cancer (UUC).[25]

3. CT imaging of thorax and abdomen (distant staging) should be performed in order to assess the presence of metastasis of abdominal lymph nodes, liver, lungs and bones.

The radiological evaluation of lymph nodes has low sensitivity and specificity; a pelvic and an abdominal lymph node are considered clinically positive when their maximum short-axis diameter are respectively higher than 8 mm or higher than 10 mm.[5] Nonetheless, a slight concordance between the clinical and the pathological N stage has been demonstrated.[26]

1.5 SURGICAL DISEASE MANAGEMENT OF MIBC

1.5.1 RADICAL CYSTECTOMY

Radical cystectomy (RC) has the aim of removing the urinary bladder, for it is the organ that contains the primary tumour.

In male patients, the surgery consists of the excision of urinary bladder, prostate, seminal vesicles, distal ureters; in 25% of the cases, an incidental diagnosis of prostate cancer is made.[27] In selected patients, whose disease is limited to the bladder and does not invade the prostate, prostatic urethra and bladder neck and who are motivated to preserve their sexual function, it is possible to perform a nerve-sparing cystoprostatectomy, not removing the neurovascular bundles in order to preserve the sexuality of the patient, with no difference in oncological outcomes.[28]

In female patients, during standard radical cystectomy the bladder, distal ureters, uterus, ovaries, annexes and anterior vaginal wall are removed. This procedure is associated with vaginal prolapse requiring other procedures in 10% of the cases[29], to consequent urinary incontinence and to a deterioration in sexual function. In addition, less than 10% of the patients effectively had an involvement of their reproductive organs, and 25% of them were finally staged as T4a.[30] To improve functional outcomes, still maintaining an oncological safety, it is possible to use a vaginal-sparing approach[31] and colposacropexy.

For both sexes, after radical cystectomy lymphadenectomy is performed. Standard lymphadenectomy[32] comprises internal and external iliac lymph nodes and obturator lymph nodes.

Radical cystectomy can be performed with an open (ORC) or robot-assisted (RARC) approach. In comparison with ORC, RARC has shown an increase in operative time, but a decrease in the length of hospital stay, in the incidence of venous thromboembolism and in transfusion rates[33], with comparable oncological outcomes and mortality. When selecting the patients for RARC, it is necessary to evaluate properly their medical history, their performance status and their fitness for surgery.[34] In particular, the patient who undergoes RARC should be able to tolerate a pneumoperitoneum lasting hours, and a Trendelenburg position with 30° head down, which is particularly challenging in the case of a low pulmonary compliance.[35] Moreover, a history of prior considerable abdominal surgery may preempt a difficult docking and adhesiolysis, thus partially contraindicating RARC.

The mortality after radical cystectomy is described as 2.1-3.2% at 30 days and 3.4-8% at 90 days[36], but it decreases in hospitals with a high volume of patients and good surgical expertise.[37]

1.5.1.1 INDICATIONS TO RADICAL CYSTECTOMY

Radical cystectomy should be planned within the first three months of the diagnosis of:

- MIBC (T2-T4a N0 M0);
- NMIBC when:
  - The risk is very high;
  - The tumour is classified as BCG-refractory, BCG-relapsing and BCG-unresponsive[38];
  - It is not possible to eradicate the disease with a TURB procedure.

BCG-refractory tumour
1. If T1 HG/G3 tumour is present at 3 months. 2. If Ta HG/G3 tumour is present after 3 months and/or at 6 months, after either re-induction or first course of maintenance. 3. If CIS (without concomitant papillary tumour) is present at 3 months and persists at 6 months after either re-induction or first course of maintenance. If patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases. 4. If HG tumour appears during BCG maintenance therapy.
BCG-relapsing tumour
Recurrence of HG/G3 tumour after completion of BCG maintenance, despite an initial response.
BCG-unresponsive tumour

BCG-unresponsive tumours include all BCG refractory tumours and those which develop T1/Ta HG recurrence within 6 months of completion of adequate BCG exposure or develop CIS within 12 months of completion of adequate BCG exposure. Adequate BCG is defined as the completion of at least five of six doses of an initial induction course plus at least two out of six doses of a second induction course or two out of three doses of maintenance therapy.
BCG-exposed tumour
Either BCG resistant (if Ta HG/G3 or CIS is present at three months evaluation after induction BCG only) or delayed relapse after adequate or inadequate BCG.
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment.

Table III[38]

1.5.1.2 ROBOT-ASSISTED RADICAL CYSTECTOMY: SURGICAL TECHNIQUE

According to the Pasadena Consensus Panel[34], the operation starts with the positioning of the patient in a head-down 30° Trendelenburg position; the legs are put in stirrups with minimal hip flexion and spread in order to accommodate the robotic surgical system; the knees' flexion forms a 30° angle.

In the Urology Clinic of the University Hospital of Padua[39], a Da Vinci X or Xi system is used in a four-arm configuration (in *figure 4*, 8 mm robotic trocars), adding to them a 12-mm assistant port (in *figure 4,* 12 mm laparoscopic trocars) and an AirSeal flow system.

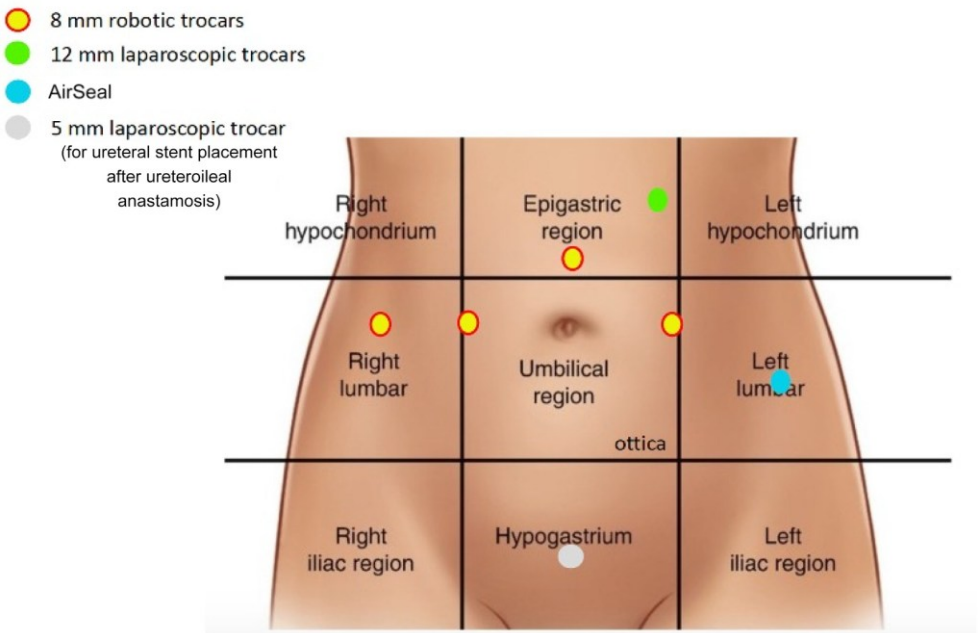

Figure 4. Port placement for RARC in Urology Clinic of the University Hospital of Padua.[39] The grey laparoscopic port is used only during the reconstructive part of the operation.

The first step of the surgery is the same for both sexes[35], and consists of the individuation and isolation of the ureters through the opening of the peritoneum covering. The ureters are then clipped with two Hem-o-lock which are positioned near to the ureterovesical junction. Then, they are cut, sending the distal ureteric margins to the pathologist for frozen section.

1.5.1.2.1 SURGICAL TECHNIQUE IN MALES

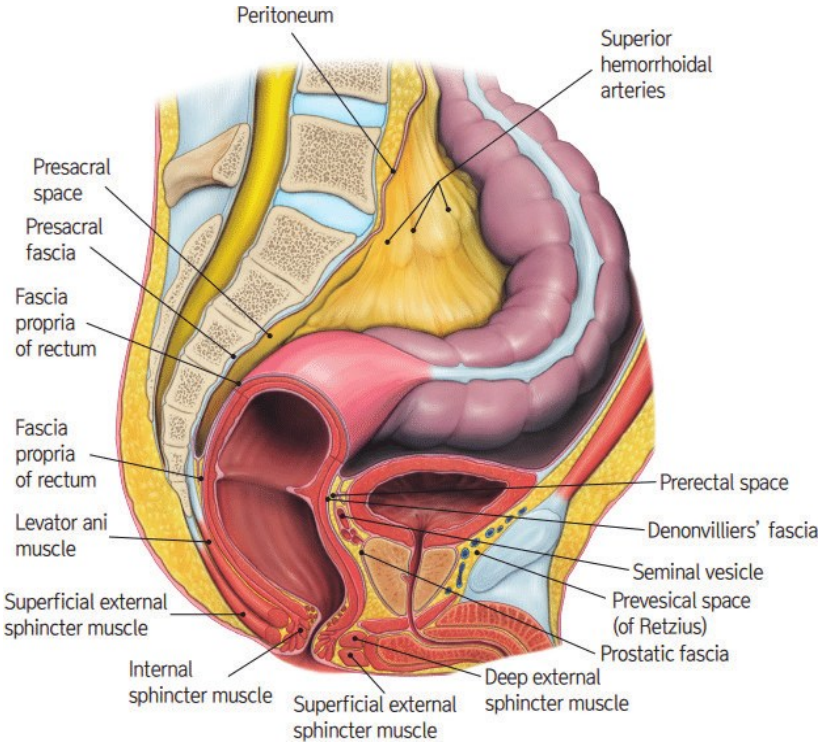

Figure 5. Anatomy of the fascia and pelvic floor in male pelvis.[40]

For male patients, the next step is to open the anterior rectal space, then identifying and exposing the seminal vesicles and the Vas Deferens. Consequently, the plane between the rectum and prostate has to be developed as distally as possible.

After that, the lateral pelvic space (space of Retzius) has to be developed, identifying the medial umbilical ligaments, incising the peritoneum lateral to them and opening it down to the endopelvic fascia. This is then opened in order to separate the prostate from the *levator ani* muscle and to isolate the prostatic apex and the dorsal vein complex.

In the following phase, the lateral pedicles of the bladder are isolated, and the superior vesicle artery and the inferior vesicle artery are divided.[35]

Then, the procedure can be continued with a nerve-sparing technique, in order to preserve the neurovascular bundles in selected patients, or with a non-nerve

sparing technique, in patients who have erectile dysfunction, or are sexually inactive, or have a bulky posterior disease.[34]

If the procedure is not nerve-sparing, the neurovascular bundles are transected on the posterior and lateral side of the prostate down to the prostatic apex. If it is nerve-sparing, the neurovascular bundles are separated from the prostate without using thermic energy and the prostate is separated from the Denonvilliers' fascia along its capsule.[35]

At this point of the surgery, the bladder is separated from the anterior abdominal wall cutting the uracus and the median umbilical ligaments and is then mobilized. The dorsal vein complex is cut and haemostasis done with a suture; the specimen is clipped under the prostatic apex and divided from the urethra; finally, a frozen section of the proximal urethral margin is sent to the pathologist, and the entire specimen is placed in a retrieval bag.

1.5.1.2.2 SURGICAL TECHNIQUE IN FEMALES

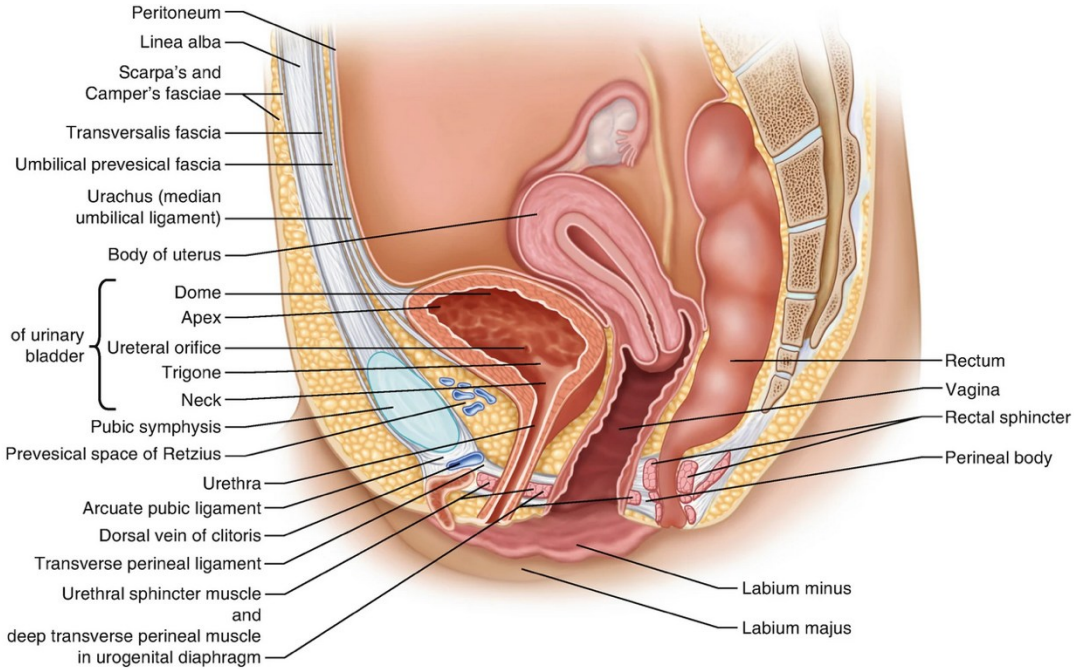

Figure 6. Anatomy of female pelvis.[41]

In females[35], from the beginning of the operation, a sponge stick or a vaginal manipulator is positioned.

What comes after the isolation and cut of the ureters is the posterior dissection, which separates and divides the uterus, the infundibulo-pelvic suspensory ligaments and the ovarian pedicles. In this case, the operation is considered non-organ-sparing.

At that point, the uterus has to be put under tension, drawing it back cranially; in this way, the vaginal apex is taken into vision and the uterus and the vaginal anterior wall are separated as they are part of the specimen. The vaginal sponge should make it possible to keep the pneumoperitoneum after the vaginal opening and it should facilitate the individuation of the cervicovaginal junction. It is important to try not to damage lateral vaginal walls, because the autonomic nerves that are responsible for sexual function lay there.

If the tumour is limited to the bladder only, it is possible to plan an organ-sparing technique, which consists of preserving the uterus, the annexes, the ovaries

and the vagina, or a vaginal-sparing technique, in which only the anterior wall of the vagina is not dissected.

The following phase of the surgery is to open the space between the vagina and the bladder and to dissect it down to the bladder's neck. Laterally, the umbilical ligaments and the round ligaments are dissected, and the vascular pedicles of the bladder are clipped and cut; after that, it is possible to continue the lateral dissection in order to reach the endopelvic fascia along the pubic bone and open it.

Then, the anterior wall of the bladder is separated from the abdominal wall with the same technique that is used in male patients, and the urethra and the dorsal venous complex are identified.

If the procedure is non-organ-sparing, the urethra and the anterior vaginal wall are cut together and form part of the specimen. On the contrary, if the procedure is organ-sparing, the anterior vaginal wall is opened and separated from the urethra, leaving the first in its place and sending the second to the pathologist. If the construction of a neobladder is planned, the urethra cut should be done just under the bladder neck, in order to improve the postoperative outcome in terms of urinary continence.

Both in an organ-sparing and in a non-organ-sparing procedure, the specimen can be isolated in a retrieval bag and removed through the natural vaginal orifice, if its dimensions are permissive. The vagina is then reconstructed with a continuous suture and it is suspended to the sacral promontory or to the pubic rami in order to prevent prolapse.[34]

1.5.1.3 LYMPHADENECTOMY

Nowadays, the standard of care is to perform a bilateral pelvic lymphadenectomy, which dissects the external and internal iliac and the obturator lymph nodes bilaterally.

A large, multi-centre, randomized, controlled trial by Lerner et al.[42] compared patients who had undergone radical cystectomy with bilateral pelvic lymphadenectomy to patients who had undergone radical cystectomy with extended lymphadenectomy, which dissects the external, internal and common iliac lymph nodes up to the bifurcation of the aorta and the presacral nodes. The follow-up showed a similar disease-free survival and overall survival in the two groups at a median of 6 years after the surgery. However, in the first 90 days after surgery, the incidence of high grade adverse events and deaths was significantly higher in the patients who had undergone extended lymphadenectomy. Consequently, the authors concluded that extended lymphadenectomy did not improve disease-free and overall survival, thus encouraging performance of bilateral pelvic lymphadenectomy after radical cystectomy in patients with localized MIBC.

1.5.2 URINARY DIVERSIONS

After radical cystectomy (the deconstructive part of the operation), it is necessary to recreate a passage between the ureters and the outside of the body (the reconstructive part of the operation). The intestinal tract and, particularly, the ileum, can be given a new function in the restoration of the urinary tract. Different urinary diversions have been developed; the choice of the technique which fits best for the patient strictly depends on their anatomy and health status, as urinary diversion is the part of the operation that generates the majority of postoperative complications.[43] Also the patient preference and the tumour characteristics should be taken into account.

Urinary diversions can be divided into non-continent (e.g., ileal conduit) and continent (e.g., orthotopic neobladders). Beyond the surgical aspects, that will be analyzed in the following paragraphs, it is also interesting to consider the psychological and social impact of this choice.[44] On one hand, non-continent urinary diversions require placement of a stoma on the abdomen of the patient, which can result in a negative perception of the patient’s body image. On the

other hand, the creation of a continent urinary diversion still has an impact on the patient's lifestyle, as it requires self-discipline in the regular emptying of the neobladder and other postoperative challenges, such as the recovery of urinary continence.

1.5.2.1 NON-CONTINENT URINARY DIVERSIONS

The simplest way to reconstruct the urinary tract is with non-continent urinary diversions. Uretero-cutaneostomy and ileal conduit are part of this category.

Uretero-cutaneostomy consists of connecting the ureters directly to the skin. It can be used in frail patients, as it reduces the length of operation, intensive care and hospital stay and it causes a lower complication rate and blood loss.[45] Nonetheless, it conveys a higher rate of stenosis of the anastomosis, hence it requires a permanent ureteral stenting with catheters that have to be replaced every 3-4 months, and, consequently, an increased risk of UTIs (Urinary Tract Infections).[46]

Another possible option is to create a uretero-ileo-cutaneostomy or ileal conduit. In this technique, a 20-cm ileal tract is isolated at a distance of at least 20 cm from the ileocaecal valve and is used to create an ileal pouch. On one side, this is connected to the skin, creating a stoma. On the other side, the ureters are anastomosed to the ileal pouch; the anastomosis can be performed using the Bricker reconstruction, that is to anastomose the ureters individually to the ileal pouch, or using the Wallace reconstruction, that is to anastomose the ureters together to the inner side of the ileal pouch[47]. The incidence of stenosis of the anastomosis with ileal conduit is much lower than with ureterocutaneostomy.

1.5.2.2 CONTINENT URINARY DIVERSIONS

The most important type of continent urinary diversion is the orthotopic neobladder. Reconstructing an orthotopic neobladder means creating a new organ that can act similarly to the original one, in the same place where the bladder was previously situated. It has no implication on the body image of the patient, who, after the surgery, should be able to regain their continence and urine flow through their own urethra.

However, to prevent serious complications and to guarantee a satisfactory outcome, it is fundamental to perform an accurate patient's selection.[48] The patient should be compliant and younger than 70 years old, and should be able to understand the essential principles of neobladder functioning. It is possible to select both male and female patients, even though it is more difficult to achieve a good functional outcome in women in terms of urinary continence, thus preserving the pelvic floor during the surgery is challenging. For this reason, the orthotopic neobladder is more frequently performed in male patients. In any case, preoperative incontinence is a contraindication to this type of urinary derivation. A good renal function (eGFR>40 mL/min) is required, due to the risk of developing hyperchloremic acidosis and other electrolyte abnormalities. In addition, intestinal diseases and previous resections and therapies should be carefully evaluated in order to avoid essential nutrients' malabsorption. Finally, from an oncological point of view, it is fundamental to obtain a specimen of the urethra that proves the absence of urothelial cancer. An urethral biopsy could be performed at the moment of the diagnosis with TURB; however, intraoperative frozen section of the resection margin constitutes the definitive response.

The configuration of an orthotopic neobladder aims to create a container that could guarantee continence, appropriate capacity and the possibility to empty it intentionally and entirely. These aims can be respectively achieved through the neobladder's low pressure, high compliance, appropriate volume and globular shape. Both in open and in robot-assisted surgery[49], a portion of the

intestinal tract is detubularised to avert episodes of simultaneous contractions of the neobladder, and folded twice. The ileum is the best choice in order to construct a neobladder, as its mobility allows it to reach the urethra without tension.[50]

The rates of choice of continent orthotopic neobladder urinary diversion are increasing, especially in high-volume hospitals, even though ileal conduit still remains the most frequently performed technique.[51]

Another possibility is to use an ileal tract in order to create a continent pouch (continent cutaneous diversion) that needs to be emptied periodically through self-catheterization.[47] However, the use of this technique is not frequent in clinical practice.

The following paragraphs will describe some surgical techniques that have been developed to create functional orthotopic neobladders during open or robot-assisted surgery.

1.5.2.2.1 VES.PA. ORTHOTOPIC NEOBLADDER

In 2016, at the Urology Clinic of the University Hospital of Padua, Dal Moro et al.[52] projected the Ves.Pa. (*Vesica Patavina*) orthotopic neobladder. It was specifically designed for the reconstructive phase of RARC respecting the ideal principles for the creation of an orthotopic neobladder that were presented in the previous paragraph.

As this thesis aims to study the Ves.Pa. neobladder, the surgical technique and the data regarding the perioperative, oncological and functional outcomes will be presented in the following chapters.

1.5.2.2.2 STUDER TECHNIQUE

The Studer technique was firstly applied in 1989 at the University of Berne[53] and, since then, it has largely been performed both as extracorporeal and intracorporeal urinary diversion.

The intracorporeal reconstruction of Studer neobladder[54] starts with a ileourethral anastomosis, selecting the part of the ileum that results easier to mobilize, at least at 30 centimetres from the ileocaecal valve.[55] Then, a 40-cm ileal segment is isolated proximally to the anastomosis, a 10-cm ileal segment is isolated distally to the anastomosis and the bowel continuity is restored. The following step is to open the ileal segment on the antimesenteric border, leaving the first proximal 10 centimetres closed in order to preserve a “chimney” for the final configuration of the neobladder. To simplify the explanation, we will identify the 10-cm proximal point as A, the 20-cm proximal point as B, the 30-cm proximal point as C, the ileourethral anastomosis point as D, and the 10-cm distal point as E, as it is shown in *figure 3.* After the detubularisation, the posterior wall of the neobladder is sutured matching the points A and E, and the points B and D together. Finally, the neobladder is folded, matching point C to points A and E, that have been previously coupled, and completing the suture of the anterior wall. At last, an ileo-ureteral anastomosis with Wallace technique is performed at the more proximal point of the chimney.

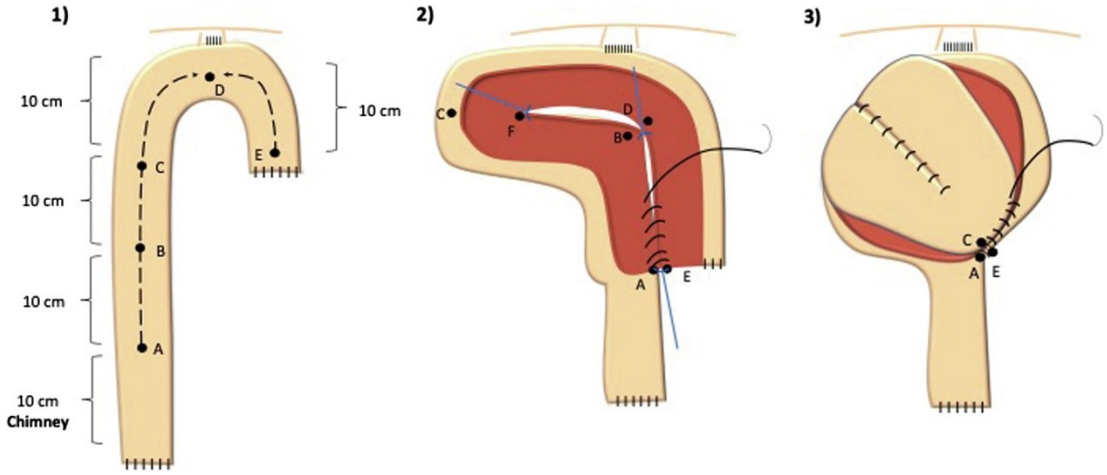

Figure 7. Studer technique: main surgical steps.[55]

The outcomes of Studer neobladder in terms of quality of life and urinary continence are reported as satisfactory.[56]

Martini et al.[57] in 2023 studied a group of male patients at 12 months after robotic surgery reporting a day-time continence with Studer neobladder of 68% and a night-time continence of 32%. They defined continence as the use of a maximum of one pad during the day and one pad during the night. Moreover, they analyzed the erectile function in the patients who underwent a nerve-sparing procedure, reporting that, at 12 months: 31% of the patients were completely potent, not needing any medication; 24% of the patients were potent, needing to use an oral phosphodiesterase type 5 inhibitor (PDE5i); 5% of the patients were able to achieve erection after an intracavernous injection; 24% of the patients were not potent; 16% of the patients were not sexually active. However, as erectile function does not depend on the reconstructive but on the demolitive part of the operation, these data regard patients after RARC with intracorporeal neobladder reconstruction with different techniques, of which Studer is one. For this reason, data on erectile function will not be reported for the following techniques of intracorporeal neobladder reconstruction.

1.5.2.2.3 HAUTMANN (W-SHAPE) TECHNIQUE

Hautmann technique[48] for open radical cystectomy starts with the isolation of a 60-cm tract of ileum at 20-25 cm from the ileocaecal valve. After restoring bowel continuity, the tract of ileum is subdivided into four branches in order to shape a W letter. The two external branches should measure approximately 5 cm more than the internal branches; these parts will later be used to form two chimneys. A suture is positioned at the passage between the first and the second branch in order to mark the part of the ileum that will be anastomosed with the urethra. Detubularisation on the antimesenteric side of the ileal tract is then performed, except for the two chimneys. After that, the posterior wall of the neobladder is closed with three sutures that connect the internal edges of

the detubularised intestine. Next, the lower third of the external edges of the detubularised intestine is sutured forming the caudal part of the anterior wall of the neobladder. Afterwards, three anastomoses are performed: the previously marked point of the ileum is anastomosed to the urethra, and each ureter is anastomosed to its respective chimney using Wallace technique. Finally, the neobladder configuration is completed with a T-shaped suture of the anterior wall.

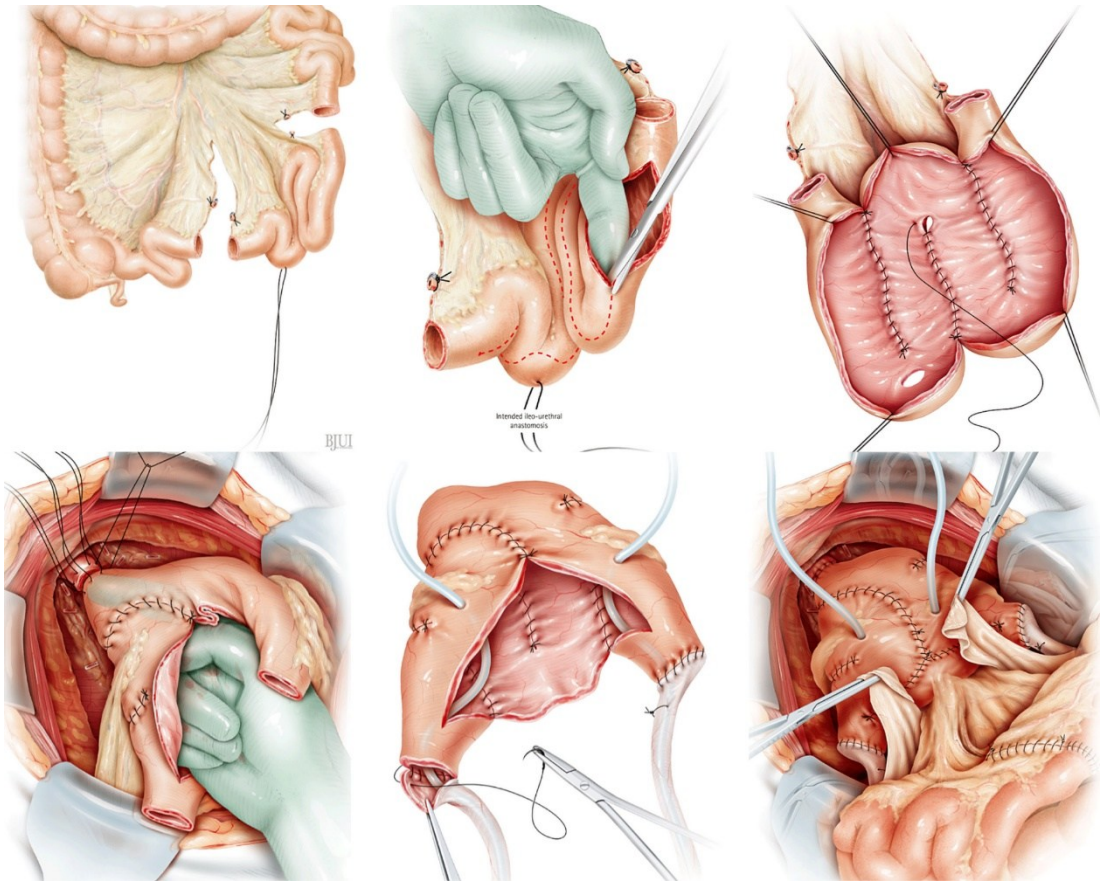

Figure 8. Hautmann technique.[48]

This technique has then been slightly modified in order to adapt it to intracorporeal reconstruction during robot-assisted surgery.[58]

A study by Hautmann et al.[59] analyzed the functional outcomes of 259 male patients from a single centre, reporting a day-time continence of 90% and a night-time continence of 82%. However, another study by Martini et al.[57]

analyzed the functional outcomes of male patients after intracorporeal robot-assisted Hautmann orthotopic neobladder and reported a day-time continence of 52% and a night-time continence of 24%.

1.5.2.2.4 Y-SHAPED NEOBLADDER

Initially, the Y-shaped neobladder[60] was designed for open radical cystectomy with the aim of shortening the duration of the operation and of preventing ileoureteral strictures. The reconstructive part starts with the isolation of a 40-cm tract of ileum, at a minimum distance of 15-20 cm from the ileocaecal valve, and with the re-establishment of intestinal continuity. Then, the isolated tract of ileum is shaped as a Y letter, forming the limbs of the letter with 6 cm of ileum for each side, and the central part with two ileal segments of 14 cm each. After that, the lowest point of the Y shape is opened in order to insert a non-absorbable mechanical stapler that is used to detubularise and match the central segments. Next, the same opening is connected to the urethral stump, creating the ileourethral anastomosis. Afterwards, each limb is anastomosed to its respective ureter and sutured to the psoas muscles in order to fix it. Instead of suturing mechanically the neobladder, it is also possible to detubularise the two ileal segments on the antimesenteric border, to suture the medial edges thus creating the posterior wall, and then to fold the lateral edges and suture them so as to create the anterior wall.[54]

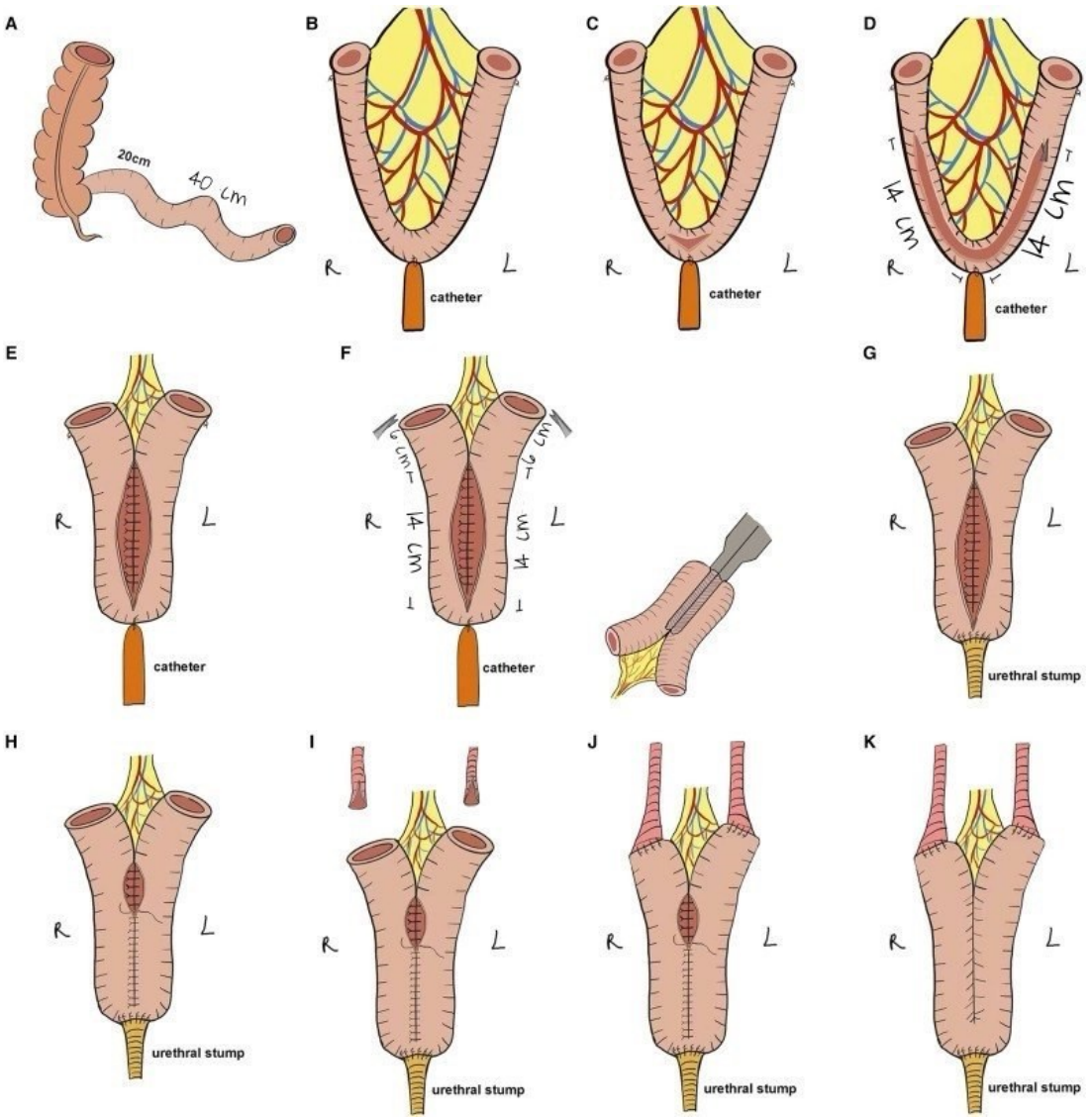

Figure 9. Y-shaped neobladder.[60]

In relation to urinary continence, defining it as the use of 0 or 1 pads during the day and 0 or 1 pads during the night, approximately 80-85% of the patients reached day-time continence at 6 and 12 months after surgery, and approximately 75-80% of the patients reached night-time continence at 6 and 12 months after surgery. No statistically significant difference in urinary continence between male and female patients was reported.

A modified technique for the Y-shaped neobladder has been developed for robotic surgery, the results of which in terms of urinary continence are

satisfactory: Mao et al.[61] report a day-time continence at 12 months of approximately 90%, and a night-time continence at 12 months of approximately 80%; Anceschi et al.[62] report a day-time continence at 12 months of 79%, and a night-time continence at 12 months of 66%.

1.5.2.2.5 FLORENCE ROBOTIC INTRACORPOREAL NEOBLADDER

Florence Robotic Intracorporeal Neobladder (FloRIN)[63] was designed in 2017 specifically for robotic surgery. Its construction starts with the isolation and section of a 50-cm tract of ileum at 20 cm proximally to the ileocaecal valve, re-establishing then the intestinal continuity. After that, the intestinal tract is shaped as an asymmetrical U letter, with the ileourethral anastomosis separating a 30-cm segment at the distal side and a 20-cm segment at the proximal side. Then, detubularisation on the antimesenteric side of the U is performed and the posterior wall of the neobladder is sutured, shaping it as an L letter orientated towards the right side of the patient. Next, the lowest part of the posterior wall is folded in order to create the neobladder neck with a 2-5 cm suture starting from the median point of the anterior wall of ileourethral anastomosis. Afterwards, the proximal side of the posterior wall of the neobladder is folded too, matching the end of the neobladder neck with a point at approximately 5 cm right to the centre of the proximal edge. The following step is the orthotopic implantation of the two ureters on each side of the anterior

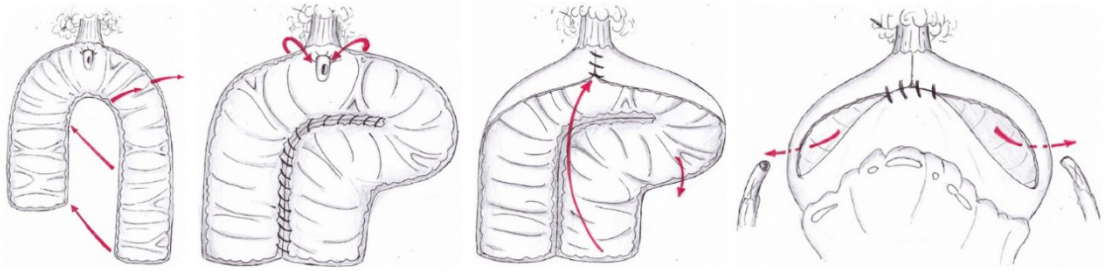

Figure 10. FloRIN neobladder.[63]

wall of the neobladder. Finally, a V-shaped suture is performed in order to complete the closure of the anterior wall of the neobladder.

Functional outcomes have been evaluated at 6 months after surgery in a single centre study by Minervini et al.[64]: they reported that 75.4% of the patients achieved day-time continence, while 65.2% of the patients achieved night-time continence. Another study by Anceschi et al.[62] reported a day-time continence rate at 12 months of 80% and a night-time continence rate of 70%.

1.5.3 COMPLICATIONS AND MORTALITY

Radical cystectomy is a major surgical intervention, for it cannot be considered free of complications. Early complications are defined as events occurring less than 30 days after the surgery, while late complications regard events taking place between 30 and 90 days after the surgery.

In a study by Yu et al.[65] Robot-Assisted Radical Cystectomy (RARC) was compared to Open Radical Cystectomy (ORC). They found that inpatient mortality was 0% for RARC and 2.5% for ORC, which was consistent with other data about ORC that estimated that its mortality rates ranged between 0.3% and 3.9%. Moreover, the complication rate was lower for RARC, and so were the use of parenteral nutrition after surgery and the blood loss. There were no differences in length of stay and completeness of lymphadenectomy. On the contrary, the negative aspects are that RARC's cost is significantly higher than ORC's one and that the operative time is higher.

In 2015, Novara et al.[66] conducted a systematic literature review which analyzed perioperative outcomes and complications of RARC. Weighted mean operative time was 340 minutes for RARC with intracorporeal conduit and 420 minutes for RARC with intracorporeal neobladder. Overall mean blood loss was 270 ml for RARC with intracorporeal conduit and 480 ml for RARC with intracorporeal neobladder; respectively, the transfusion rate was 14.7% and 7%. They found that surgical experience was able to improve the results in

terms of reduction in overall diversion time, operative time, in-hospital stay and late complication rates.

After RARC with intracorporeal conduit diversion, the complication rates were 67% before the 30th postoperative day, 22% between the 30th and the 90th postoperative day, and 59% at the 90th postoperative day. Reoperation rates were 39% before the 30th postoperative day, 19% between the 30th and the 90th postoperative day, and 25% at the 90th postoperative day. Reported mortality rate was 1.7% within the 90th postoperative day.

After RARC with intracorporeal continent diversion, the complication rates were 45.7% before the 30th postoperative day, and 30% between the 30th and the 90th postoperative day. Reoperation rates were 17% before the 30th postoperative day, 16% between the 30th and the 90th postoperative day, and 33% at the 90th postoperative day. Reported mortality rate was 1% before the

30th postoperative day, 1.7% between the 30th and the 90th postoperative day, and 2.7% at the 90th postoperative day.

According to the Pasadena Consensus Panel[34], the length of stay after RARC with intracorporeal urinary derivation ranged between 4 and 10 days, and the readmission rate ranged between 17% and 60%.

Considering the types of complications, Shabsigh et al.[67] found that, after radical cystectomy, the patients suffered from:

- Gastrointestinal complications (29%): ileus, small bowel obstruction, constipation, *C. difficile* colitis, gastrointestinal bleeding, anastomotic bowel leak, diarrhoea, emesis;
- Infectious complications (25%): urinary tract infections, fever of unknown origin, sepsis, abscess, pyelonephritis, urosepsis, gastroenteritis, cholecystitis, diverticulitis;
- Wound complications (15%): infection, dehiscence, seroma;
- Genitourinary complications (11%): ureteral obstruction, renal failure, urinary leak, urinary retention, parastomal hernia, haematuria, stomal ischaemia;
- Cardiac complications (11%): arrhythmia, myocardial infarction, hypertension, hypotension, congestive heart failure, angina;
- Pulmonary complications (9%): pneumonia, respiratory distress, pleural effusion, atelectasis, pneumothorax;
- Bleeding (9%): anaemia requiring transfusion, wound haematoma, postoperative bleed other than GI;
- Thromboembolic complications (8%): deep venous thrombosis, pulmonary embolism, superficial phlebitis;
- Neurological complications (5%): delirium/agitation, peripheral neuropathy, TIA, loss of consciousness, vertigo, seizures;
- Miscellaneous (3%): lymphocele, dehydration, psychological illness, decubitus ulcer, acidosis, others;

– Surgical (1%): vascular injury, bowel injury, incisional hernia, retained foreign body.

To predict the occurrence of postoperative morbidity after ORC, gender, an ASA score higher than 2 and the type of urinary diversion can be considered significant[67], whereas age, ASA score, Charlson Comorbidity Index, blood transfusion and BMI can be evaluated as predictors of postoperative complications after RARC.[66]

In terms of oncological outcome, the RAZOR trial[68] compared the results of RARC and ORC at 2 years after the surgery. There was no statistically significant difference in progression-free survival across all cancer stages in the two groups; disease progression was defined as any documented recurrence, or death from any cause. Moreover, the rate of recurrence was similar between the two groups, and there was no evidence of metastases at the port sites. Consequently, the hypothesis that the use of ports, the pneumoperitoneum and the loss of tactile feedback could increase cancer peritoneal seeding was proven false. In conclusion, RARC was demonstrated to be non-inferior to ORC in terms of progression-free survival and not to increase the risk of positivity of margins or peritoneal carcinomatosis.

Moreover, a significant difference in terms of blood loss, transfusion rate and median length of hospital stay was found, with RARC showing lower rates, while the median operative time was still significantly longer for RARC than for ORC, even though only RARC with extracorporeal urinary diversions were included in this study.

A 3-year follow-up of the patients who participated in the RAZOR trial was made[69], confirming the data about progression-free survival and cancer recurrence. The progression-free survival at 3 years was 68.4% in patients who underwent RARC and 65.4% in patients who underwent ORC, and the overall recurrence was respectively 26% and 26.3%. In addition, patients who were aged more than 70 years old, who experienced high-grade complications and who had a poor performance status, a high grade tumour and positive surgical

margins were identified as potential predictors of 36-month progression-free survival and overall survival.

1.6 PERIOPERATIVE SYSTEMIC THERAPY

1.6.1 CHEMOTHERAPY

Chemotherapy is a systemic treatment that aims to stop the growth of cancer cells in the whole body. For bladder cancer, it can be used as a single therapy in patients with a locally advanced (T4b, N2, N3) or metastatic (M1) disease or as a combined therapy along with radical cystectomy.

In 2023, von der Maase et al.[70] compared in a large, randomized, multi-centre study the two most-used chemotherapy schemes: gemcitabine plus cisplatin (GC) and methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) as a single therapy. They found that overall survival, time to progressive disease, time to treatment failure and overall tumour response rates were similar for both schemes. However, gemcitabine plus cisplatin showed a lower toxicity, better tolerability and safety, and lower rates of high-grade adverse events, such as neutropenic sepsis or severe mucositis. Moreover, the patients who were treated with GC were able to recover weight, felt less fatigue and had a better performance status during the treatment. In conclusion, GC was demonstrated to be an effective treatment for bladder cancer and to be a safer alternative to MVAC, thus becoming the standard of care for bladder cancer.

According to Galsky criteria[71], a patient is considered eligible for cisplatin when they have an ECOG PS of 0 or 1, a normal renal function (creatinine clearance>60 ml/min), a NYHA (New York Heart Association) heart failure class

of I or II, no or mild hearing loss (grade 0 or 1) and no or mild peripheral neuropathy (grade 0 or 1).

1.6.1.1 NEOADJUVANT CHEMOTHERAPY

The chemotherapy regimen is considered neoadjuvant when it is administered prior to the surgery. It aims to eliminate the micrometastases, which are estimated to be present in 25% of the patients at the moment of the diagnosis of bladder cancer.

Yin et al.[72] demonstrated that the use of platinum-based neoadjuvant chemotherapy followed by radical cystectomy can improve the survival rates of 8% at 5 years, so the number needed to treat is 12.5. They suggested that neoadjuvant chemotherapy should become the standard of care for bladder cancer.

The advantage of neoadjuvant chemotherapy is that the patient has higher possibilities to tolerate a systemic treatment before the surgery. However, it causes a delay in receiving the surgical treatment, which can result in a poorer outcome in some patients. For example, the ones whose disease started as a NMIBC and then progressed to MIBC (secondary MIBC) had lower response rates to chemotherapy and worse overall cancer-specific outcomes following cisplatin-based neoadjuvant chemotherapy in a study by Pietzak et al.[73]

Nevertheless, Arora et al.[74] compared patients who underwent radical cystectomy alone (RC only) and patients who underwent neoadjuvant chemotherapy and radical cystectomy (NAC + RC) and found that the rate of complications after the surgery is not influenced by the use of neoadjuvant chemotherapy. In particular, they analyzed the length of hospital stay, the rate of complications at 30 and at 90 days after surgery and the rates of surgical re-intervention and re-hospitalization and did not come across any significant difference. They also observed that the patients in the NAC + RC group underwent RARC with a neobladder reconstruction more frequently than the

others. They underlined that, even if the use of NAC increased from 11% to 48% during 11 years, it should be implemented in a higher number of patients.

1.6.1.2 ADJUVANT CHEMOTHERAPY

After the surgery, an adjuvant chemotherapy should be programmed for the patients who had a pathological staging of pT3 or pT4 or a nodal positivity (pN+), if they can still tolerate it in spite of postoperative morbidity.

A systematic review and meta-analysis by Burdett et al.[75] demonstrated that the use of adjuvant chemotherapy can result in a clear advantage for the patients. At 5 years, the absolute improvements in overall, recurrence-free and metastasis-free survival were estimated at 6%, at 11% and at 8% respectively. Furthermore, an observational study by Galsky et al.[76] compared adjuvant chemotherapy and observation after radical cystectomy in patients with a pT3, pT4 or pN+ disease, concluding that there is a consistent association between adjuvant chemotherapy and improved overall survival.

In addition, Sternberg et al.[77] analyzed the outcomes of different timings of adjuvant chemotherapy in a randomized trial, comparing two groups of patients with a pT3-pT4, pN+ pathological diagnosis after radical cystectomy. The first group of patients received an immediate treatment with 4 cycles of GC or high-dose MVAC; the second one received 6 cycles of deferred chemotherapy at relapse. This trial evidenced that, at 5 years, overall survival was similar in the

two groups, while progression-free survival was significantly longer for patients in group 1.

1.6.2 IMMUNOTHERAPY

Immunotherapy is a type of cancer treatment that aims to activate the immune system against cancer cells.

For the discovery of the therapeutical use of immune checkpoint inhibitors, James P. Allison and Tasuku Honjo were awarded the Nobel Prize in Physiology and Medicine in 2018. T-cell activation can be blocked by regulatory mechanisms, which are necessary in a physiological state. However, cancer cells can take advantage of these mechanisms in order to block the immune system. The basic function of immune checkpoint inhibitors is to surpass the block of T-cell, thus making it possible for the immune system to activate against cancer cells.[78]

Different immune checkpoint inhibitors acting on the PD-1/PD-L1 regulatory system have been approved for the treatment of urothelial carcinoma, e.g. atezolizumab, avelumab, durvalumab, nivolumab, pembrolizumab. PD-1 is a molecule which is expressed on activated T lymphocytes; its interaction with PD-L1, a molecule that can be expressed by cancer cells, reduces T-cell activation. Consequently, the use of a monoclonal antibody which blocks either PD-1 or PD-L1 can result in an increase in the function of T cells, hence it can make them able to induce tumour rejection.[78]

1.6.2.1 PEMBROLIZUMAB

Pembrolizumab is an anti-PD-1 humanized monoclonal antibody.

Bellmunt et al.[79] studied the possible use of pembrolizumab as a second-line therapy in patients who were progressing after platinum-based chemotherapy. They compared a group of patients treated with pembrolizumab as a single

therapy, without considering if their tumour expressed PD-L1 or not, and a group of patients treated with chemotherapy (paclitaxel, docetaxel or vinflunine). They concluded that the first group had a significantly longer overall survival (by approximately 3 months), a similar progression-free survival and fewer adverse events related to treatment.

Powles et al.[80] investigated a possible use of pembrolizumab as a first-line therapy, alone or combined with GC chemotherapy, comparing it with the use of GC chemotherapy alone. Their randomized trial on 1,010 patients with advanced urothelial carcinoma found that, as a first line, either pembrolizumab alone or combined with chemotherapy, showed no significant difference from the use of chemotherapy alone in terms of progression-free survival and median overall survival. The most common adverse effect caused by chemotherapy was anaemia, while pembrolizumab caused diarrhoea, fatigue and hyponatremia.

There is still no evidence for the use of pembrolizumab as a neoadjuvant therapy in combination with surgery.

1.6.2.2 AVELUMAB

Avelumab is an anti PD-L1 humanized monoclonal antibody.

Its use as a maintenance therapy after platinum-based chemotherapy was studied by Grivas et al. in the JAVELIN Bladder 100 Phase 3 Trial[81]. After the completion of first-line chemotherapy and no evidence of progression, the patients were randomized to avelumab maintenance therapy plus best supportive care or best supportive care alone. They found that the maintenance therapy with avelumab was advantageous in terms of median overall survival and progression-free survival for cisplatin-eligible and cisplatin-ineligible

patients after chemotherapy, regardless of PD-L1 positivity of the tumour, thus encouraging its use as a standard of care.

1.6.2.3 ENFORTUMAB VEDOTIN

Enfortumab vedotin (EV) is an antibody-drug conjugate. The antibody is totally human and its molecular target is nectin-4, a transmembrane receptor which is involved in cancer cell migration, adhesion, and proliferation and is expressed in urothelial cancer cells.[82] The antibody is conjugated to monomethyl auristatin E (MMAE), a synthetic antimitotic agent that blocks the polymerization of tubulin, thus blocking the cell cycle and causing apoptosis.[83]

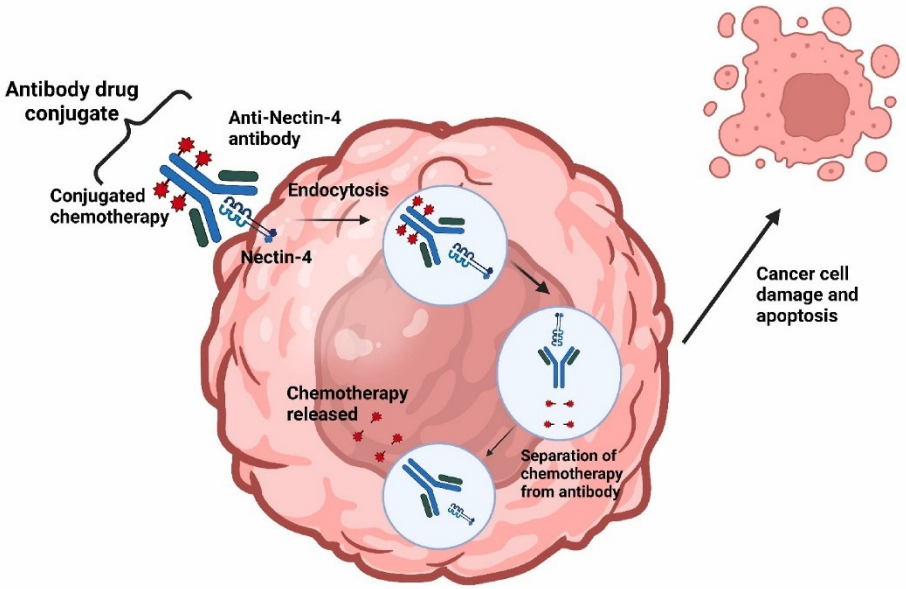

Figure 11. Functioning of an antibody-drug conjugate (ADC).[82]

Powles et al. in the EV-302/KEYNOTE-A39 trial[84] compared the use of enfortumab vedotin plus pembrolizumab (EV+P) and platinum-based chemotherapy as a first line in patients with locally advanced or metastatic urothelial carcinoma. At a median follow-up of 29.1 months, there was a significant advantage in the EV+P group in terms of median progression-free survival and overall survival in spite of the patients' platinum eligibility, with a stratified hazard risk of 0.48. The duration of response was of approximately

24 months; some patients obtained a complete clinical remission, and the probability of maintaining it at 2 years was 74.3%.

Consequent to this trial, EV+P should be offered as first-line treatment in patients with locally advanced or metastatic urothelial carcinoma, also considering that it can be administered to all the patients, without the restrictions of platinum eligibility. However, at the moment it has not been approved by AIFA, hence the standard care in Italy[17] is the use of cisplatin plus gemcitabine in cisplatin-eligible patients as a neoadjuvant, adjuvant or first line systemic treatment, and the use of avelumab as maintenance therapy for 12 months. In cisplatin-ineligible patients, carboplatin plus gemcitabine is the first choice; platinum-ineligible patients can be treated with checkpoint inhibitors. The use of EV+P is limited to the patients who are enrolled in a clinical trial or for compassionate use.

2. OBJECTIVE

This study aims to explore perioperative, oncological and functional outcomes of 100 patients (83 men and 17 women) who underwent a Robot-Assisted Radical Cystectomy with Ves.Pa. Neobladder reconstruction in the Urology Clinic of the University of Padua between 2021 and 2025.

The data analysis intends to investigate: perioperative complications, postoperative complications and late complications; oncological outcomes after the surgery and at follow-up; functional outcomes in terms of urinary continence at follow-up.

3. MATERIALS AND METHODS

3.1 DESIGN, SETTING AND PARTICIPANTS

From April 2021 to December 2025, 100 patients underwent RARC with Totally Intracorporeal Neobladder reconstruction using the Ves.Pa. technique.[39] Over 170 variables per case were collected in a prospective study. All patients were staged with contrast-enhanced CT imaging of the thorax and abdomen, and all staging was performed within 2 months before surgery.

Included patients had either non-metastatic MIBC, or NMIBC in the setting of BCG-unresponsive, BCG-refractory, BCG-relapsing or BCG-exposed disease. Also, high-grade tumours that could not be managed with endoscopic resections were considered potential candidates for a Ves.Pa. neobladder.

Patients older than 75 years of age, those presenting a locally advanced or metastatic disease, and those with urethral involvement were excluded from the study.

The ERAS (Early Recovery After Surgery) protocol was applied to all the patients with early mobilization and early postoperative feeding with liquid or solid diets.

3.2 SURGICAL PROCEDURE

All the procedures were performed in the Urology Clinic of the University Hospital of Padua by experienced surgeons, using a da Vinci X or Xi system. RARC and lymphadenectomy were performed respecting all the surgical indications given by the Pasadena Consensus meeting[34] and the Ves.Pa. technique was performed according to the Stage 2a IDEAL Report indications.[39]

The surgical technique to create the Ves.Pa. neobladder[39] starts with the detection of a part of the ileum that can easily reach the urethral stump, at a

minimum distance of 20 cm from the ileocaecal valve; this part is pulled close to the urethral stump and sutured, creating a low tension anastomosis.

The second step is to identify a 10-cm segment distal to the anastomosis and a 30-cm segment proximal to the anastomosis using two 10-cm haemostatic strips, which are positioned proximally and distally to the urethro-ileal anastomosis, and one 20-cm haemostatic strip, which indicates the most proximal 20-cm segment; in addition, the 20-cm point is marked with a stay suture. Then, the entire 40-cm ileal loop is resected, and a latero-lateral ileal anastomosis is performed in order to restore bowel continuity.

The third step is to detubularise the 40-cm isolated ileal loop along the antimesenteric border; then, shape the neobladder with two successive foldings. In the first folding, the medial margins at the 40-cm and 20-cm marks are aligned and two sutures are performed, starting from the 20-cm mark and running distally towards the 10-cm mark and proximally towards the 30-cm mark. The second folding reproduces the steps of the first one, this time aligning the medial margins at the 30-cm and 0-cm points and performing two

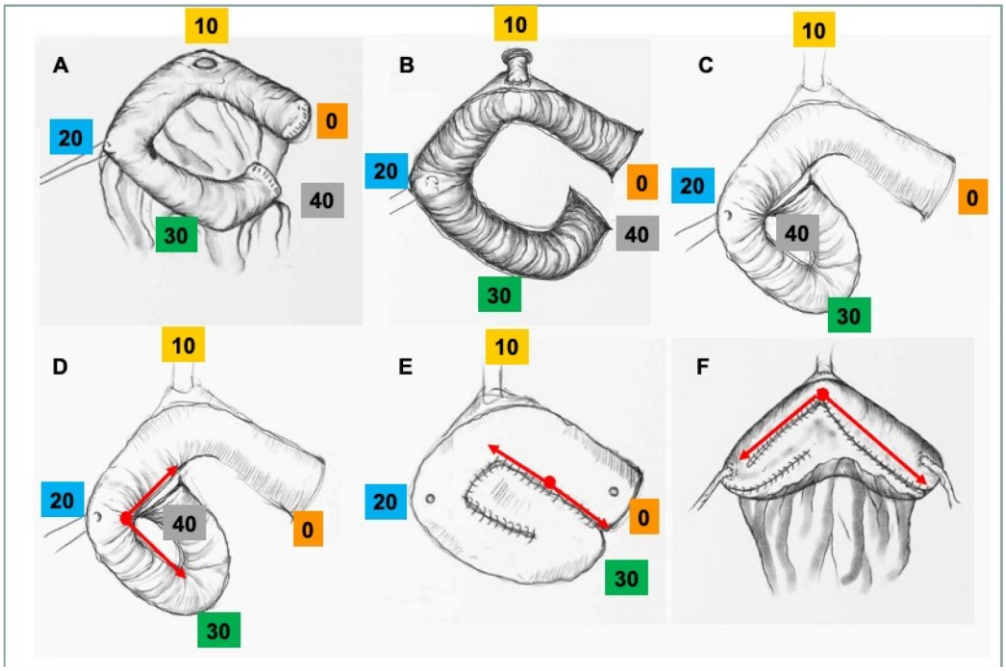

Figure 12. Surgical technique to create Ves.Pa. neobladder.[39]

sutures, starting from the middle of the suture line and running towards the 0-cm mark cranially, and towards the 10-cm mark caudally.

At this point, the ureters are reimplanted on their respective sides of the neobladder with two ureteral-neobladder anastomoses.

Finally, the neobladder is folded again, matching its lateral margins, and it is closed with two sutures starting in the median line and running towards the ureter reimplantation.

3.3 DATA COLLECTION

Data about the perioperative course were recorded through the consultation of the digital medical case files of the patients.

Preoperative data included:

- demographics: age, gender;
- preadmission medical history: BMI, performance status (ECOG PS), comorbidities (CCI), smoking status, prior abdominal surgery;
- bladder cancer history: preoperative clinical staging, neoadjuvant chemotherapy.

Perioperative data included:

- blood tests before and after the surgery;
- ASA score;
- operative time;
- intraoperative complications;
- estimated blood loss;
- perioperative transfusion rate;
- postoperative course: mobilization, postoperative feeding, recovery of normal bowel function, complications, length of stay;
- early postoperative complications;
- complications after discharge within the 90^{th} day after the surgery.

Postoperative complications were evaluated with Clavien-Dindo Classification.[85]

TABLE 1. Classification of Surgical Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications
	Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

ANNALS OF SURGERY

Figure 13. Clavien-Dindo classification.[85]

Data from the pathological report (pT, pN, histological type, lymphatic, vascular and perineural invasion, surgical margins and, in male patients, concomitant prostate cancer) were also analyzed.

The functional outcomes were evaluated during the follow-up with the administration of validated questionnaires in their recognized Italian translation: to evaluate urinary symptoms and their consequences on the quality of life of the patients, the International Prostate Symptom Score (IPSS)[86] was used; to evaluate urinary continence, the International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form (ICIQ-UI SF)[87] was used.

3.4 STATISTICAL ANALYSIS

Continuous variables are reported as the median and interquartile range (IQR). Categorical variables are reported as the frequency and percentage. Univariable logistic regression was used to evaluate the existence of predictors of complications after the surgery. Recurrence-free survival was analyzed with

a Kaplan-Meier estimator. All statistical analyses were performed with SPSS for Macintosh v.30 (IBM Corp., Armonk, NY, USA).

4. RESULTS

4.1 PATIENTS' CHARACTERISTICS

The following table summarizes the main preoperative and anamnestic features of the patients who participated in the study.

Variables	
Median age at surgery (IQR)	64 (56 – 67)
Male gender, n (%)	83 (83%)
Median BMI (kg/m^2) (IQR)	25.5 (24.2 – 27.7)
AA-CCI, median (IQR)	2 (2 – 3)
Previous abdominal surgery, n (%)	41 (41%)
ASA class II or III, n (%)	93 (93%)
Clinical T stage, n (%) - Tis - Ta - Tx - T1 - T2 - >T2	 6 (6%) 11 (11%) 4 (4%) 8 (8%) 68 (68%) 1 (1%)
Clinical N+ stage, n (%)	8 (8%)
HG urothelial cancer, n (%)	94 (94%)
Neoadjuvant chemotherapy	49 (49%)

Table IV. Patients' characteristics. IQR=Interquartile Range; n=absolute number; BMI=Body Mass Index; AA-CCI=Age Adjusted Charlson Comorbidity Index; ASA=American Society of Anesthesiology; HG=High Grade.

The total number of patients was 100, of which 83 (83%) were males and 17 (17%) were females. The median age at surgery was 64 [IQR 56 – 67].

The median BMI was 25.5 [IQR 24.2 – 27.7]. When the BMI ranges between 18.5 and 24.9, it is considered normal; when it ranges between 25.0 and 29.9, it indicates an overweight status.

The median age-adjusted Charlson Comorbidity Index was 2 [IQR 2 – 3]. 41 patients (41%) had undergone previous abdominal surgery.

93 patients (93%) were classified with an ASA score II or III.

The preoperative clinical T stage was Tis for 6 patients (6%), Ta for 11 patients (11%), Tx for 4 patients (4%), T1 for 8 patients (8%), T2 for 68 patients (68%), and higher than T2 for 1 patient (1%).

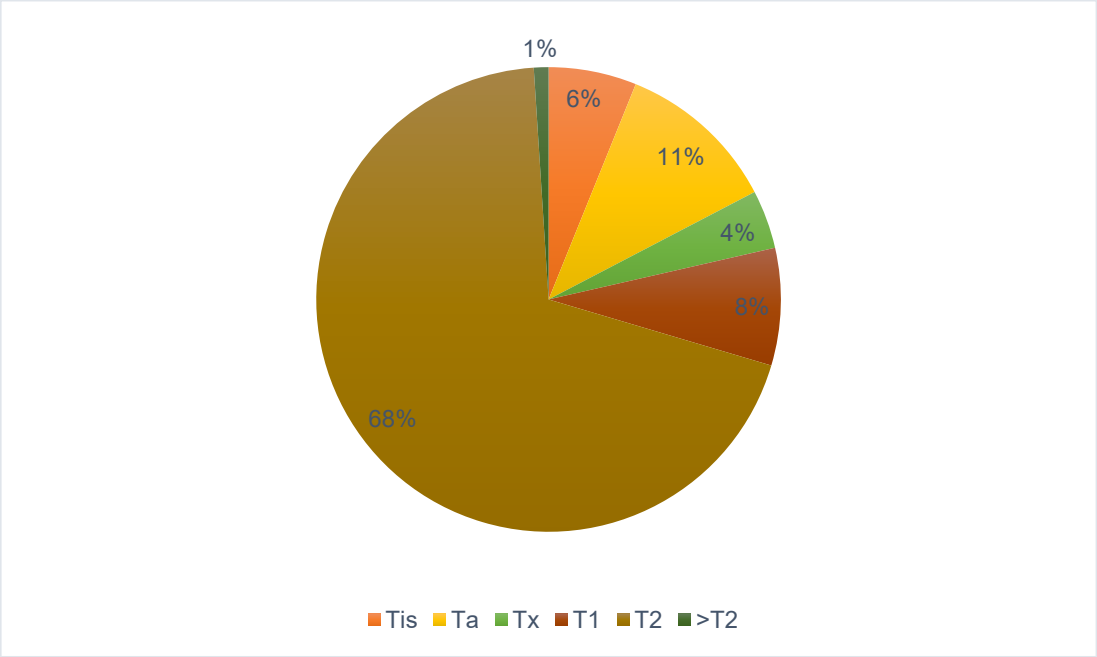

Table V. Pie chart showing the preoperative clinical T stage distribution.

The preoperative clinical N stage showed the positivity of at least one lymph node in 8 patients (8%).

The great majority of patients (94 patients, 94%) were diagnosed with a high-grade urothelial cancer.

49 patients (49%) underwent neoadjuvant chemotherapy.

4.2 INTRAOPERATIVE DATA

The following table reports the data regarding the surgical operation of Robot-Assisted Radical Cystectomy with Totally Intracorporeal Ves.Pa. Neobladder.

Variables	
Operative time (min), median (IQR)	400 (333 – 475)
Blood loss (ml), median (IQR)	400 (200 – 600)
Intraoperative blood transfusions, n (%)	11 (11%)
Intraoperative complications, n (%)	2 (2%)
Intensive care unit admission, n (%)	30 (30%)

Table VI. Intraoperative data.

The median operative time was 400 minutes [IQR 333 – 475], with a median blood loss of 400 ml [IQR 200 – 600].

11 patients (11%) required intraoperative blood transfusions, 2 patients (2%) experienced intraoperative complications, and 30 patients (30%) were admitted to the intensive care unit after the surgery.

4.3 PERIOPERATIVE DATA

The following table shows data about the postoperative course.

Variables	
Nasogastric tube removal (POD), median (IQR)	0 (0 – 0)
Mobilization (POD), median (IQR)	1 (1 – 2)
Passage of flatus (POD), median (IQR)	2 (2 – 3)
Passage of stool (POD), median (IQR)	4 (3 – 5)
Liquid diet (POD), median (IQR)	2 (1 – 3)
Regular diet (POD), median (IQR)	3 (2 – 4)
Median length of stay, days (IQR)	8 (7 – 14)

Table VII. Perioperative data. POD=Post-Operative Day.

The nasogastric tube was removed on the same day of the surgery (POD 0) for all the patients.

The patients received early mobilization after the surgery: the median postoperative day for mobilization was day 1 [IQR 1 – 2].

The intestinal passage of flatus occurred on POD 2 [IQR 2 – 3], and the passage of stool on POD 4 [IQR 3 – 5].

The patients started feeding with a liquid diet on POD 2 [IQR 1 – 3], and with a regular diet on day 3 [IQR 2 – 4].

The median length of stay was 8 days [IQR 7 – 14].

4.4 EARLY AND LATE POSTOPERATIVE COMPLICATIONS

In this paragraph, the results about postoperative complications, evaluated with the Clavien-Dindo Classification, will be presented.

The complications that occurred in the first 30 days after the surgery are defined as early postoperative complications.

As shown in the bar chart below, 45% of the patients did not suffer from any complication; 18% of the patients experienced grade 1 complications; 31% of the patients had grade 2 complications; 6% of the patients experienced grade 3 complications. No one suffered from grade 4 complications and no one died (grade 5 complication) in the first 30 postoperative days.

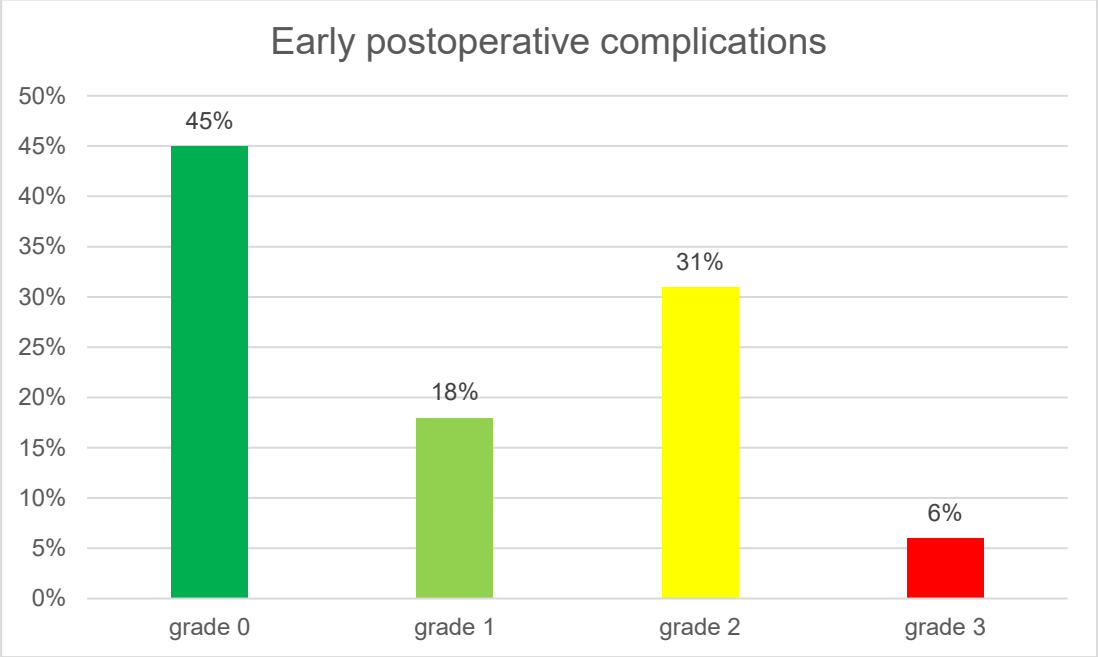

Table VIII. Bar chart showing the distribution of early postoperative complications in Clavien-Dindo grades.

Grade 3 early postoperative complications were the following:

- Uretero-vagina fistula (1%):
- Urinary leakage requiring nephrostomy tube placement (4%);
- Uretero-ileal anastomosis stricture requiring nephrostomy (2%);
- Lymphocele requiring percutaneous drainage (2%).

The complications that occurred in the first 90 days after the surgery are defined as late postoperative complications.

As shown in the bar chart below, 45% of the patients did not suffer from any complication; 15% of the patients experienced grade 1 complications; 32% of the patients had grade 2 complications; 7% of the patients experienced grade 3 complications. No one suffered from grade 4 complications and no one died (grade 5 complication) in the first 90 post-operative days.

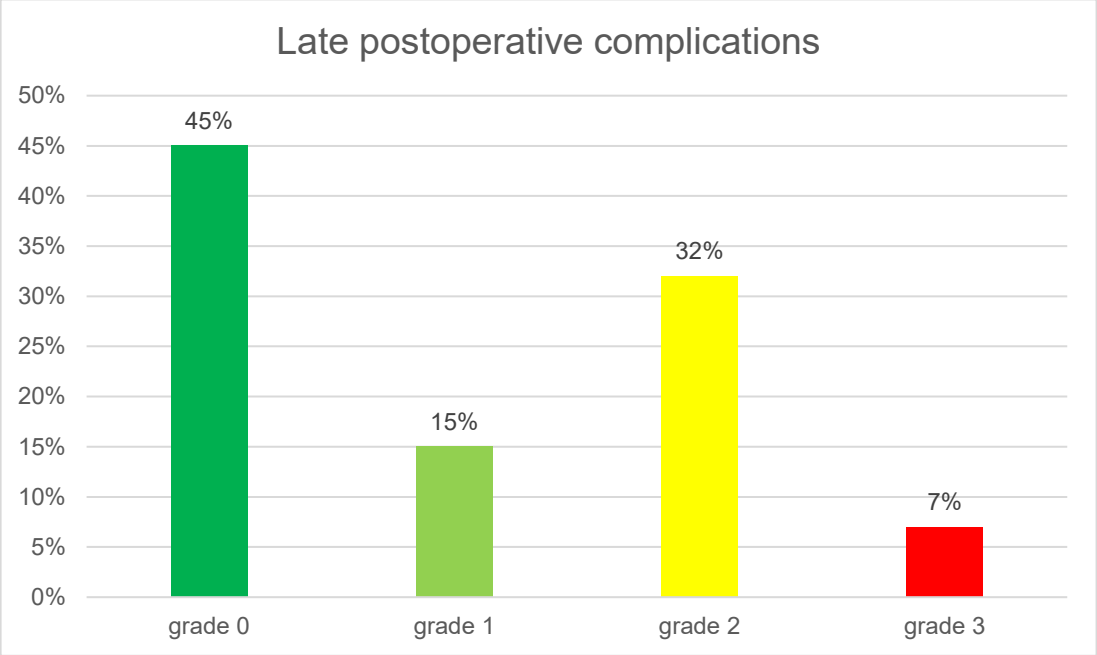

Table IX. Bar chart showing the distribution of late postoperative complications in Clavien-Dindo grades.

4.5 LATE COMPLICATIONS

Late complications are defined as complications that occurred more than 90 days after the surgery.

After RARC with the Ves.Pa. Neobladder, 5% of the patients developed an incisional hernia and 7% of the patients experienced complications related to the uretero-ileal anastomosis.

4.6 PREDICTORS OF COMPLICATIONS

Univariable logistic regression was used to investigate the existence of factors that could predict the development of complications after the surgery.

Variables	All 0-90 days complications			High-grade 0-90 days complications		
	OR	95% IC di OR	P value	OR	95% IC di OR	P value
Age	0.94	0.89 – 1.0	0.07	0.93	0.85 – 0.99	0.04*
BMI	0.99	0.89 – 1.1	0.93	0.97	0.82 – 1.1	0.69
CCI	0.89	0.63 – 1.2	0.5	0.7	0.43 – 1.2	0.22
Smoking						
Former	Ref	–		Ref	–	
Yes	0.73	0.2 – 1.8	0.33	1.0	0.2 – 4.6	0.4
No	0.58	0.26 – 2.1	0.55	1.9	0.42 – 8.3	0.97
NAC	1.1	0.46 – 2.7	0.83	2.2	0.64 – 9	0.22

Table X. Univariate logistic regression for all types of complications and high-grade complications.

In particular, age, BMI, Charlson Comorbidity Index, active smoking and neoadjuvant chemotherapy were evaluated as possible predictors of all types of complications and high-grade complications. The association between age and high-grade complications was the only one that resulted to be statistically significant ($p<0.05$), hence age was identified as a possible predictor of high-grade complications. It was not possible to demonstrate a correlation between the other variables and the occurrence of complications after surgery.

4.7 PATHOLOGICAL DATA

The following table summarizes the data from the pathological reports on the surgical specimen.

Variables	
Histological subtype, n (%)	
- Urothelial	91 (91%)
- Squamous	1 (1%)
- Micropapillary variant	3 (3%)

- Plasmocytoid variant	1 (1%)
- Mesenchymal	1 (1%)
pT stage, n (%)	
- pT0	32 (32%)
- pTis	15 (15%)
- pTa	1 (1%)
- pT1	12 (12%)
- pT2	25 (25%)
- pT3	13 (13%)
- pT4	1 (1%)
Median number of removed nodes (IQR)	15 (11 – 21)
pN+ stage, n (%)	12 (12%)
Median number of positive nodes (IQR)	2 (1 – 2)

Table XI. Pathological data.

First of all, analyzing the histological subtype of the tumour, it was found that the great majority of patients (91 patients, 91%) were diagnosed with an urothelial subtype, 1 patient (1%) was diagnosed with a squamous subtype, 3 patients (3%) presented a micropapillary variant, 1 patient (1%) presented a

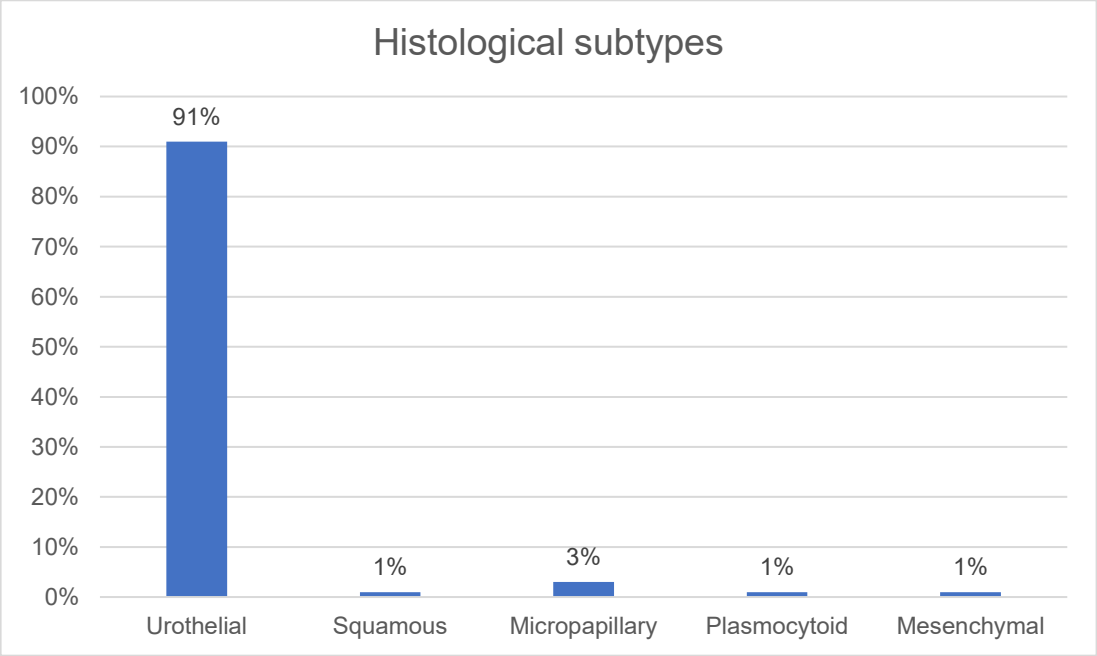

Table XII. Bar chart showing the distribution of the histological subtypes.

plasmocytoid variant, and 1 patient (1%) was diagnosed with a mesenchymal histological subtype.

About the pathological T stage, 32 patients (32%) were classified as a pT0 stage, 15 patients (15%) as a pTis, 1 patient (1%) as a pTa, 12 patients (12%) as a pT1, 25 patients (25%) as a pT2, 13 patients (13%) as a pT3 and 1 patient (1%) as a pT4.

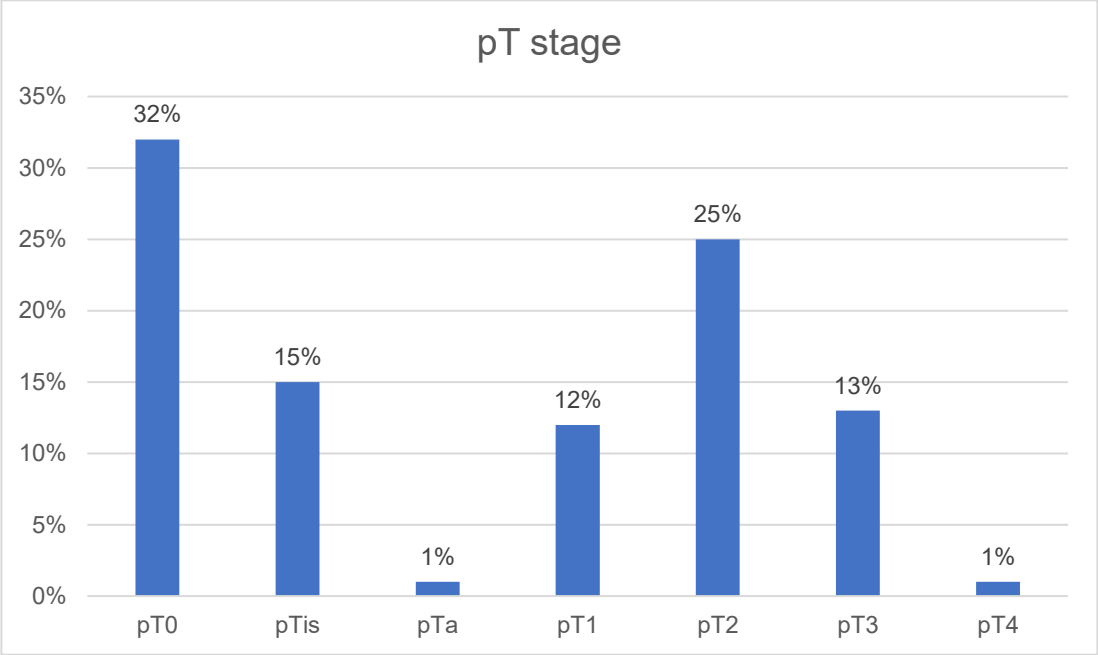

Table XIII. Bar chart showing the distribution of the pathological T stages.

The median number of removed nodes was 15 [IQR 11 – 21]. 12 patients (12%) were diagnosed with a positive pathological N stage; the median number of positive nodes was 2 [IQR 1 – 2].

The following bar chart illustrates some additional pathological findings regarding the presence of a concomitant CIS (carcinoma in situ), lymphovascular invasion (LVI), positive surgical margins (PSM), and a concomitant prostate cancer (PCA).

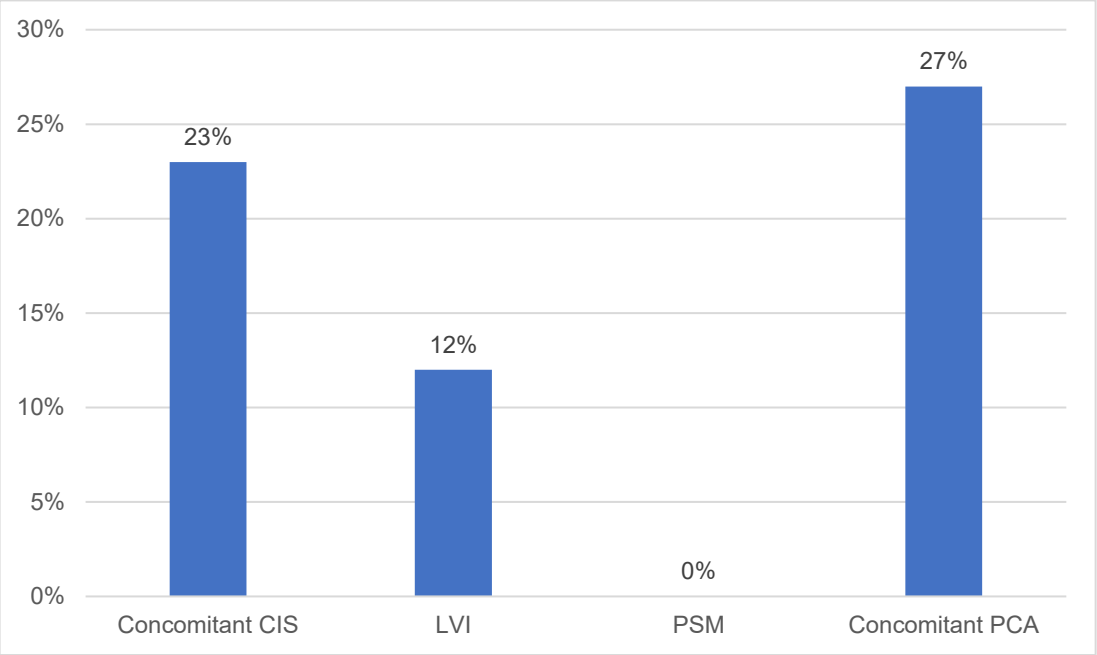

Table XIV. Bar chart showing the distribution of some additional pathological findings.

23% of the patients received a pathological diagnosis of a concomitant CIS. In 12% of the patients, at the moment of the surgery, the tumour had already invaded the lymphatic and vascular vessels. No one had a positive surgical margin (0%). 27% of the patients were accidentally diagnosed with concomitant prostate cancer.

4.8 ONCOLOGICAL OUTCOMES

The oncological outcomes were evaluated with a follow-up at a median distance of 11 months [IQR 7 – 23] from the surgery.

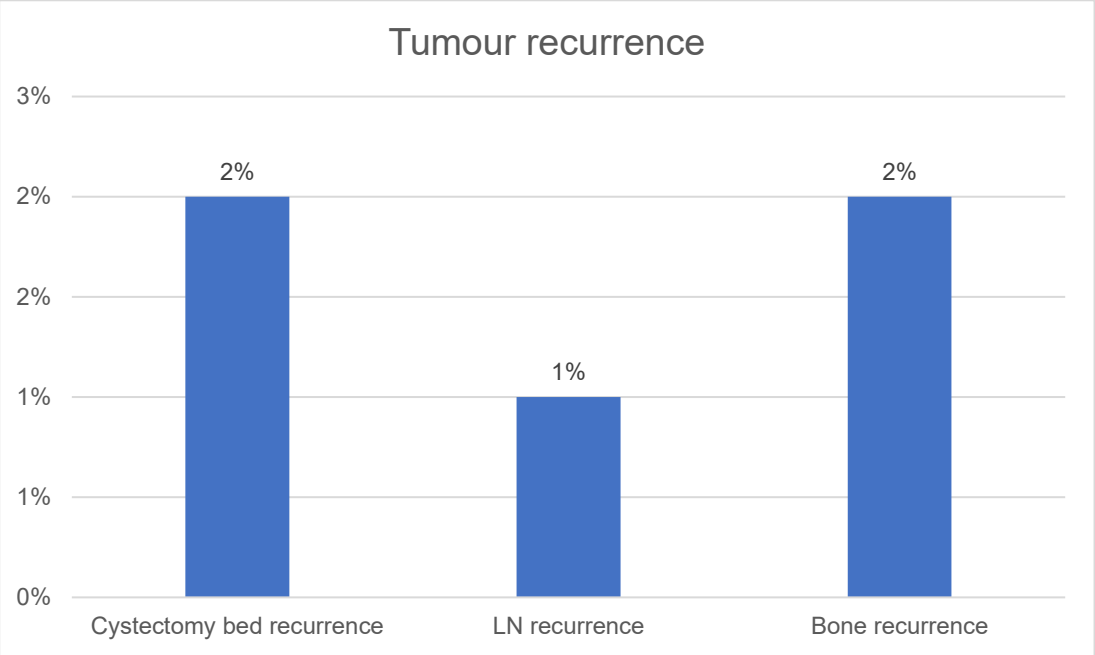

Table XV. Bar chart showing the localization of tumour recurrence.

14% of the patients received adjuvant therapies.

As it is shown in the table above, 2% of the patients had a recurrence of the tumour on the cystectomy bed, 1% had nodal recurrence, and 2% had bone recurrence.

It was estimated with a Kaplan-Meier curve that recurrence-free survival was 90% at a 12-month follow-up, and 84% at a 36-month follow-up.

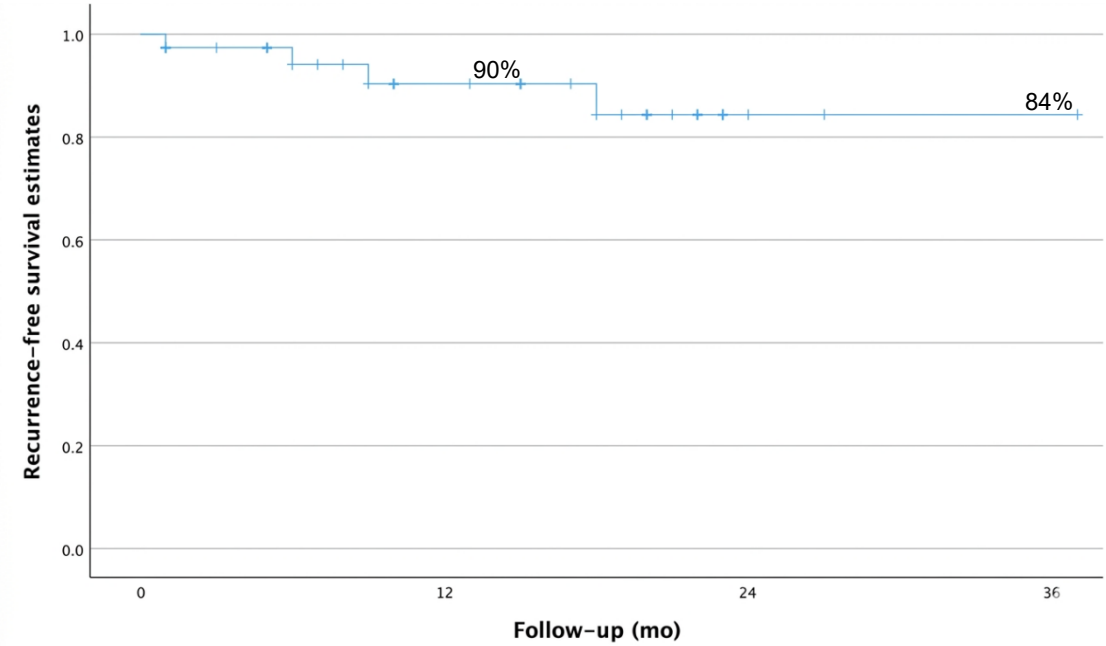

Table XVI. Kaplan-Meier estimator showing recurrence-free survival.

4.9 FUNCTIONAL OUTCOMES

At a median follow-up of 11 months [IQR 7 – 23], the IPSS and ICI-Q UI questionnaires were administered to the patients in order to assess in an objective and recognized way their urinary symptoms and their urinary continence.

4.9.1 IPSS

The following pie chart reports the IPSS total scores achieved by the patients at the follow-up after RARC with the Ves.Pa. Neobladder.

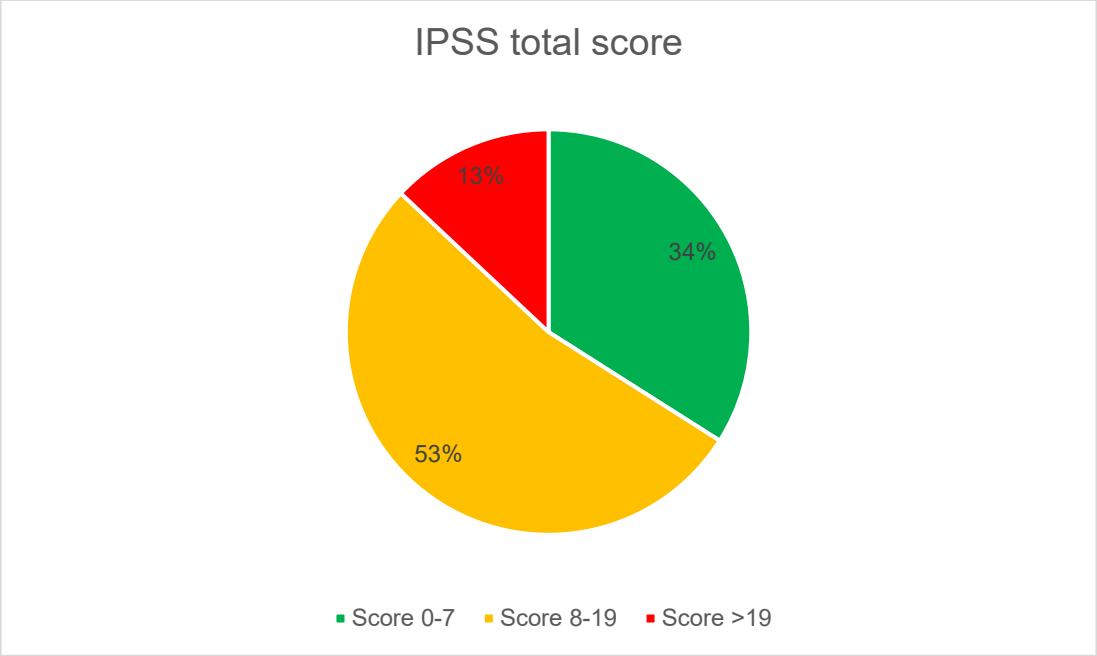

Table XVII. Pie chart showing the distribution of the patients' IPSS total score.

The three score groups indicate the severity of urinary symptoms:

- Score 0-7: mild urinary symptoms;
- Score 8-19: moderate urinary symptoms;
- Score >19: severe urinary symptoms.

Given that, the majority of the patients (53%) showed a moderate urinary symptomatology, 34% of the patients a mild one, and 13% of the patients a severe one.

The following bar chart shows the results of the IPSS score about quality of life (QoL).

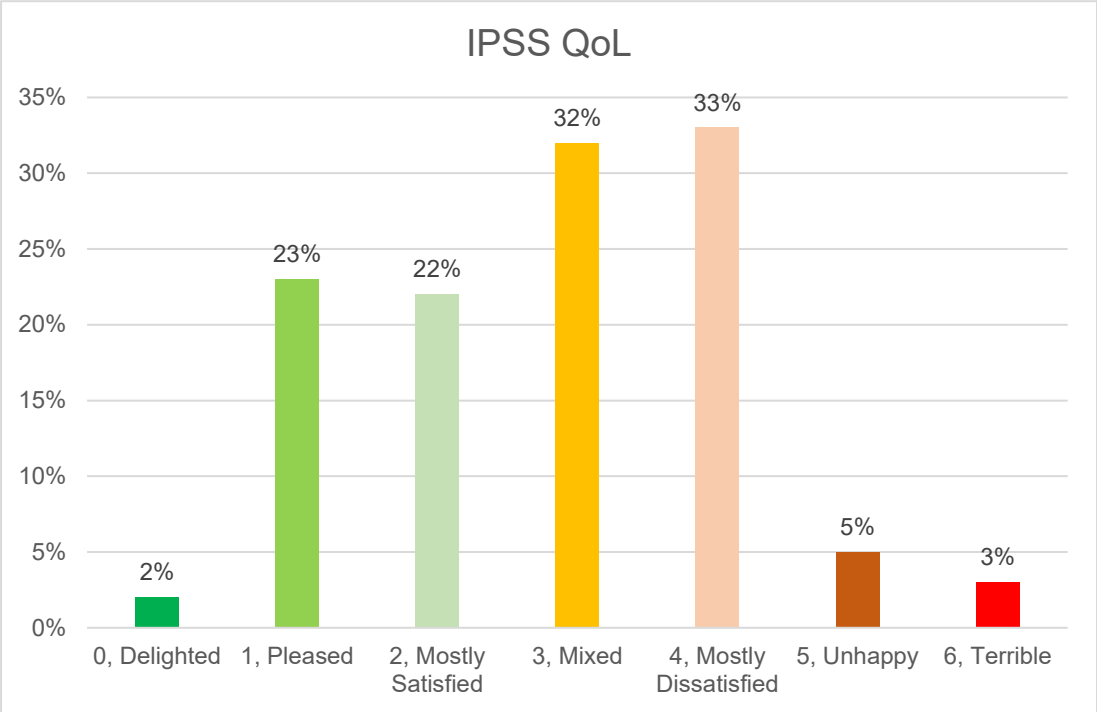

Table XVIII. Bar chart showing the distribution of the IPSS QoL score results.

The patients' feelings about the impact of their urinary symptoms on their quality of life were the following: 2% of the patients felt delighted; 23% of the patients felt pleased; 22% of the patients felt mostly satisfied; 32% of the patients had mixed feelings; 33% of the patients felt mostly dissatisfied; 5% of the patients felt unhappy; 3% of the patients felt terrible.

4.9.2 ICIQ-UI SF

The following bar chart resumes the distribution of the patients' ICIQ-UI total score at follow-up.

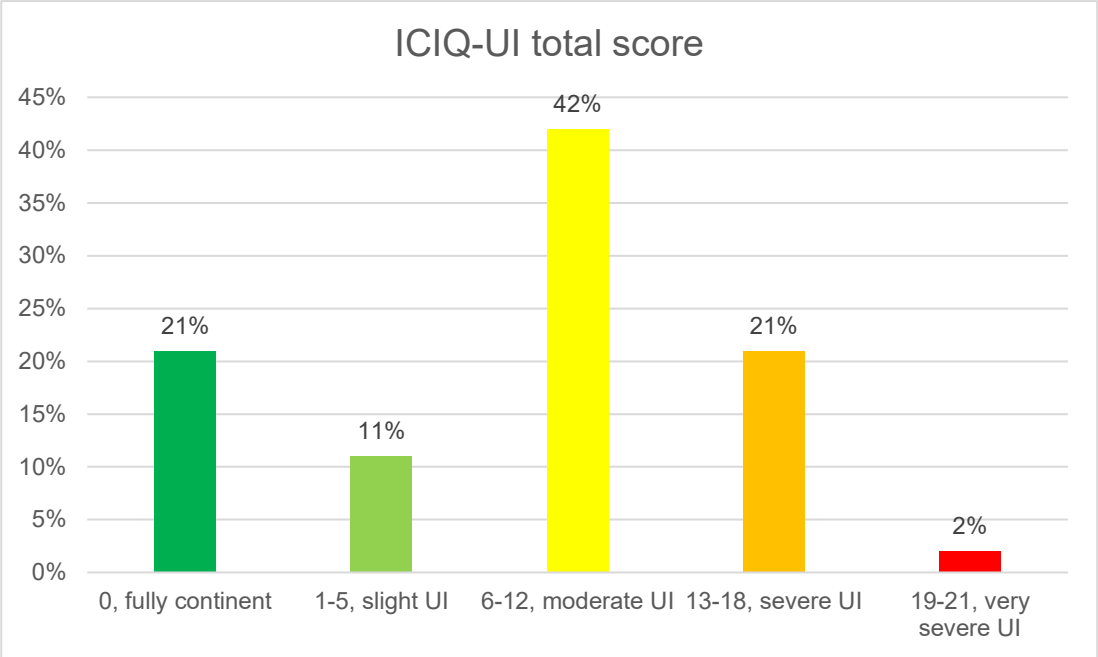

Table XIX. Bar chart showing the distribution of the patients' ICIQ-UI total score at follow-up. UI=Urinary Incontinence.

21% of the patients scored 0, thus demonstrating that they are fully continent.

11% of the patients' score ranged between 1 and 5, so they experienced a slight urinary incontinence.

The largest group of patients (42%) scored from 6 to 12 points, and their urinary incontinence was moderate.

Then, 21% of the patients had a severe urinary incontinence (score 13-18), and 2% of the patients had a very severe urinary incontinence (score 10-21).

The following bar chart shows the distribution of the answer to the question: “How often do you leak urine?”

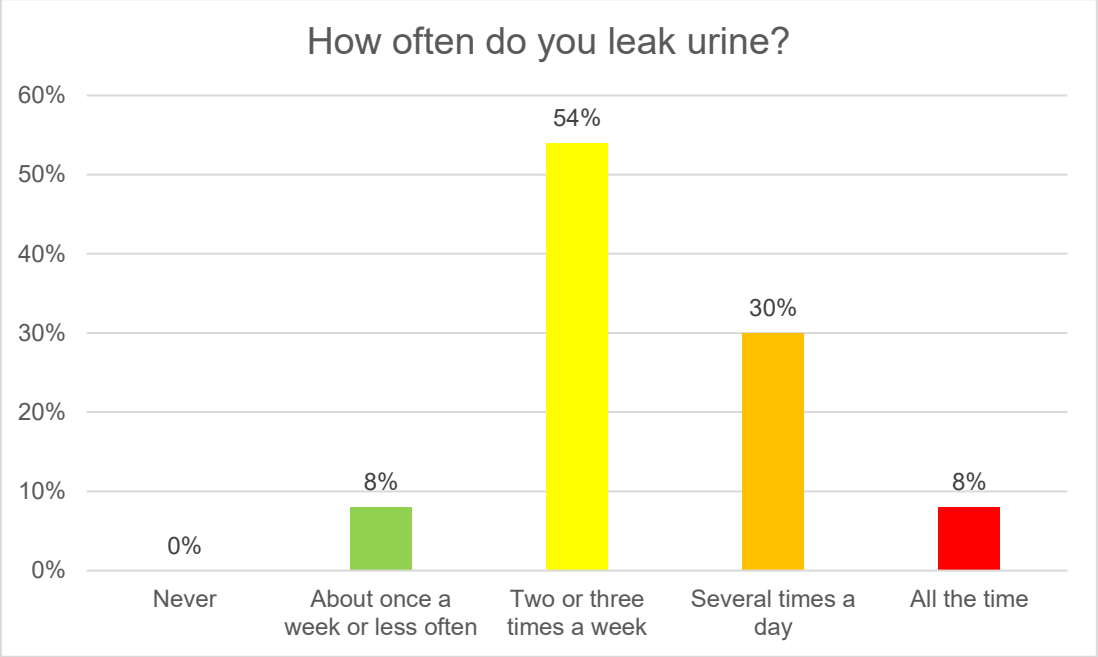

Table XX. Bar chart showing the distribution of the data about the answers to the question: “How often do you leak urine?”.

The majority of patients (54%) leaked urine two or three times a week, 30% of the patients leaked urine several times a day, 8% of the patients leaked urine all the time and 8% of the patients leaked urine about once a week or less often.

The following bar chart illustrates the connection between urine leakage and some daily activities. The question was: “When do you leak urine?”

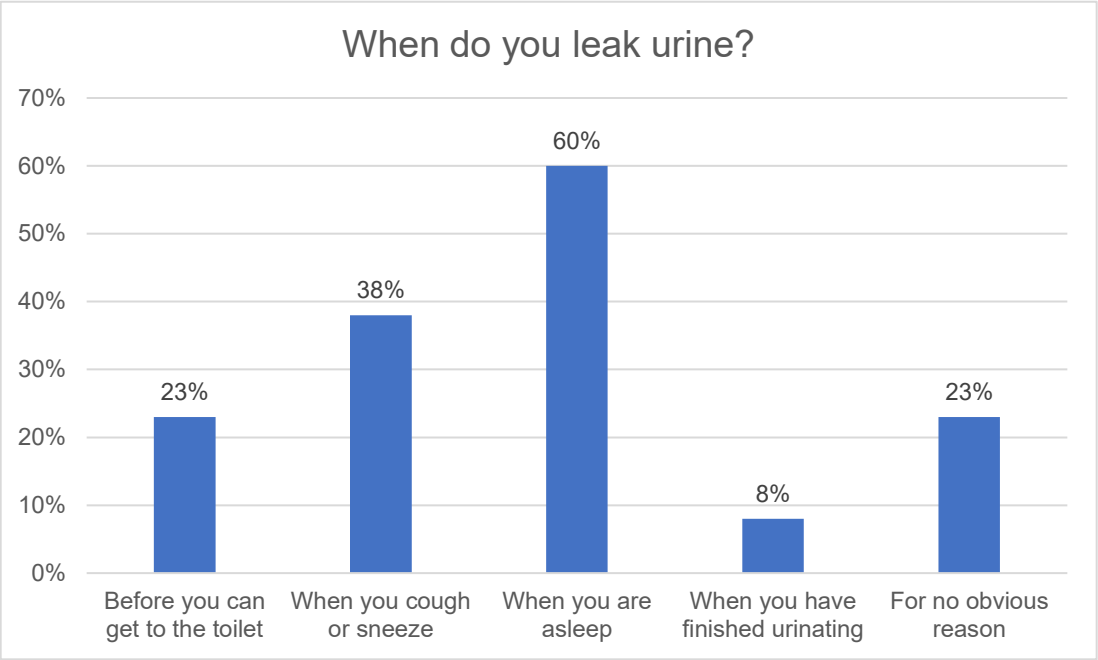

Table XXI. Bar chart showing the distribution of the answers to the question: "When do you leak urine?".

The majority of patients (60%) leaked urine when they were asleep, 38% of the patients leaked urine when they coughed or sneezed, 23% of the patients before they could get to the toilet, 23% of the patients did not associate an obvious reason to urine leakage and 8% of the patients leaked urine when they had finished urinating.

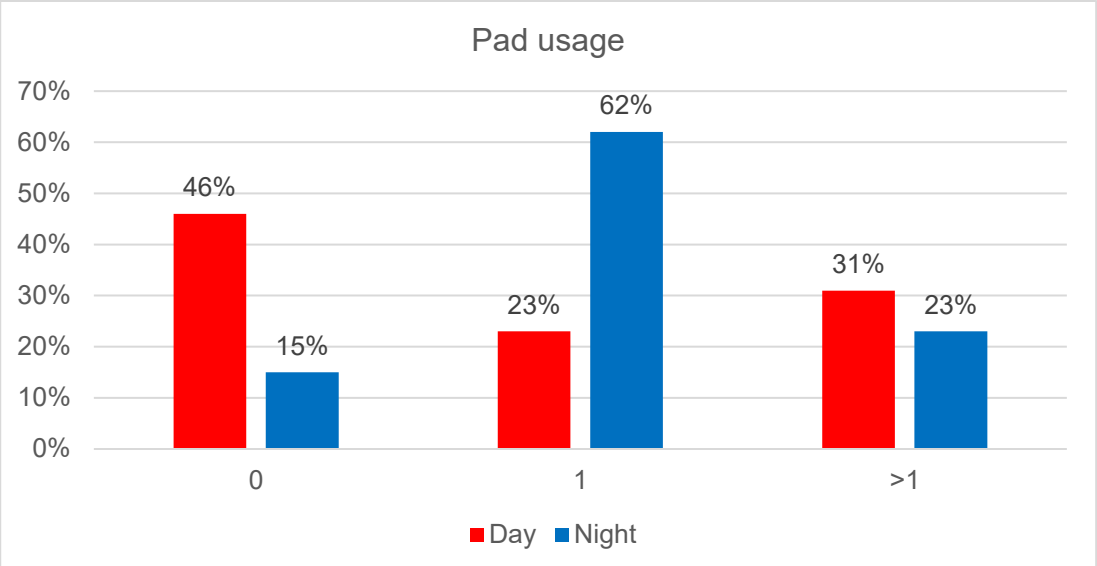

Table XXII. Bar chart showing the distribution of pad usage during the day and during the night.

Regarding pad usage, during day-time 46% of the patients did not use pads (0 pads), 23% of the patients used 1 pad, and 31% of the patients used more than one pad (>1 pad). During night-time, 15% of the patients did not use pads (0 pads), 62% of the patients used 1 pad, and 23% of the patients used more than one pad (>1 pad).

The median time to recover complete urinary continence after the surgery was 6 months [IQR 2 – 12].

5. DISCUSSION

In this study, the perioperative, oncological and functional outcomes of 100 patients were evaluated and compared with the best available literature on RARC with an intracorporeal neobladder.

Regarding intraoperative data, a systematic review by Novara et al.[66] found that, for RARC with intracorporeal neobladder, weighted mean operative time was 420 min (range: 420 – 450 min), overall mean blood loss was 480 ml (range: 225 – 500 ml), with a transfusion rate of 7% and no intraoperative complications. The data presented in this study are consistent with these figures: the operative time (median: 400 minutes; IQR 333 – 475) and the blood loss (median: 400 ml; IQR 200 – 600) were slightly better than the literature, while the rates of intraoperative blood transfusions (11%) and intraoperative complications (2%) were slightly worse.

The median length of stay was 8.5 days (range: 8 – 9) in the systematic review[66], and 8 days (IQR 7 – 14) in our study.

The perioperative data showed a successful application of the ERAS protocol, with median nasogastric tube removal just after the surgery (POD 0), median mobilization at postoperative day (POD) 1, median start of liquid diet at POD 2, and median start of regular diet at POD 3. The median time to bowel movements was POD 2 for the passage of flatus and POD 4 for the passage of stools. These data are aligned to the ones reported by the literature about RARC with extracorporeal derivations.[66]

Novara et al.[66] also described postoperative complication rates in RARC with intracorporeal neobladder. They found a rate of 19% (range: 12 – 33%) for low grade (Clavien-Dindo grades 1-2) early complications, a rate of 13.5% (range:

13 – 15%) for low grade late complications, a rate of 28% (range: 15 – 33%) for high grade (Clavien-Dindo grades 3-4) early complications and a rate of 18% (range: 12 – 21%) for high grade late complications. Moreover, they reported mortality rates of 1% in the first 30 days after the surgery and of 1.7% from the 31st day to the 90th day after the surgery.

In our series, the rates of high-grade complications and mortality dropped: 6% of grade-3 early complications, 7% of grade-3 late complications, no grade-4 early and late complications, and no mortality within the 90th day after the surgery were recorded. However, there were higher rates of low-grade complications, both in the early ones, which affected 49% of the patients, and in the late ones, which affected 47% of the patients; this fact should be taken into account for future improvements, but it could also be related to a high accuracy in data collection.

In conclusion, data about postoperative complications are encouraging, resulting both from surgical expertise and from the strict patient selection.

Through univariate logistic regression, the impact of various factors (BMI, Charlson Comorbidity Index, active smoking and neoadjuvant chemotherapy) on all and high-grade postoperative complications within the 90th POD was analyzed and did not show any statistically significant association. Nonetheless, decreasing age (OR=0.93) was identified as a predictor of high-grade complications. On the contrary, different studies[67,88] found that increasing age (OR>1) could be considered a predictor of high-grade complications. Consequently, our finding is not in agreement with the literature and needs to be reconfirmed in larger analyses.

About the oncological outcomes of the treatment, not one of the patients had positive surgical margins, which guarantees oncological radicality. 14% of the patients had a locally advanced (pT3-pT4) tumour at the moment of the

surgery, and 14% of the patients received adjuvant therapies after the surgery. In spite of that, the tumour recurrence rate was 5%. In addition, 27% of the patients received a concomitant diagnosis of prostate cancer, which is in agreement with the rate of 25% reported by the literature.[27]

In our series, recurrence-free survival was 90% at 12-month follow-up and 84% at 36-month follow-up. These results are brilliant when compared with the literature: in the RAZOR trial[68], progression-free survival at 24-month follow-up was 72.3% and 68.4% at 36-month follow-up[69]. Once again, this result can be partially motivated by the limited number of patients who participated in our study and by the strict selection criteria.

In order to assess the functional outcomes of the Ves.Pa. neobladder, IPSS and ICIQ-UI SF questionnaires were administered to the patients at a median follow-up of 11 months.

The IPSS total score ranged between 8 and 19 points in the majority (53%) of patients, indicating the presence of moderate urinary symptoms. The patients' feeling about the impact of their urinary symptoms on their quality of life (QoL) was evaluated through the IPSS QoL score: 47% of the patients had positive feelings (felt delighted or pleased or mostly satisfied), 32% of the patients had mixed feelings, and 41% of the patients had negative feelings (felt mostly dissatisfied, unhappy or terrible) about it.

The ICIQ-UI total score indicated that 42% of the patients had moderate urinary incontinence, 32% of the patients were fully continent or had slight urinary incontinence, and 23% of the patients had severe or very severe urinary incontinence. The majority of the patients (54%) leaked urine two or three times a week, but a considerable number of them (38%) leaked urine several times a day or all the time. The most frequent moment when the patient leaked urine was during sleep (60%).

Defining urinary continence as the use of 0 or 1 pad, we found that 69% of the patients achieved day-time continence, and that 77% of the patients achieved night-time continence. These results can be compared to the functional outcomes in terms of urinary continence of other neobladder techniques. For the Studer neobladder, Martini et al.[57] reported a day-time continence of 68% and a night-time continence of 32% at 12-month follow-up; for the modified robotic Hautmann neobladder, they reported a day-time continence of 52% and a night-time continence of 24%. For Y-shaped neobladder, Mao et al.[61] report a day-time continence at 12 months of approximately 90%, and a night-time continence at 12 months of approximately 80%; Anceschi et al.[62] report a day-time continence at 12 months of 79%, and a night-time continence at 12 months of 66%. For FloRIN neobladder[62], at 12-month follow-up, day-time continence was 75.4% and night-time continence 65.2%.

In conclusion, results on urinary continence and its impact on the patients' quality of life are acceptable but improvable.

It is also important to underline the limitations of our study.

First of all, these results are preliminary; hence, further studies will be necessary to confirm them.

Then, the limited number of patients and the strict selection criteria question the possibility of making inferences from the results. In addition, this also limited the statistical significance of the univariate logistic regression.

Moreover, the surgical operations were performed by different surgeons: each one of them had a different experience with the surgical technique and was at a different point of the learning curve, thus making intraoperative data less homogeneous.

In conclusion, the objectives for future research are twofold: on the one hand, inclusion criteria should be expanded with the use of new neoadjuvant

therapies in order to increase the number of enrolled patients; on the other hand, long-term follow-ups should be designed to treat and study potential late complications.

6. CONCLUSIONS

Robot-Assisted Radical Cystectomy with Totally Intracorporeal Neobladder using the Ves.Pa. technique for the treatment of bladder cancer is giving promising results from different points of view.

In terms of intraoperative and perioperative course, our data are aligned to the ones reported by the literature about RARC with intracorporeal derivations.

Regarding postoperative complications, the rate of high-grade complications in our study was very low and the mortality in the first 90 post-operative days was nil. These results are better than the best available literature and are a guarantee of the accuracy of the surgical operation and of the expertise of the surgeons.

The oncological outcomes are good: oncological radicality was respected, with clear surgical margins in all patients; given the limitations of our study, recurrence-free survival was better than the literature.

The functional results are acceptable, especially if compared with the ones of other neobladder techniques.

In conclusion, our findings align with current literature in terms of perioperative, oncological and functional outcomes. These favourable results support its continued use and, possibly, warrant an investigation into expanding its application.

7. REFERENCES

1. Global Cancer Observatory: https://gco.iarc.who.int/today/en

2. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum. 2004;83:1-1438. PMID: 15285078; PMCID: PMC4781536.

3. van Osch FH, Jochems SH, van Schooten FJ, Bryan RT, Zeegers MP. Quantified relations between exposure to tobacco smoking and bladder cancer risk: a meta-analysis of 89 observational studies. Int J Epidemiol. 2016 Jun;45(3):857-70. doi: 10.1093/ije/dyw044. Epub 2016 Apr 20. PMID: 27097748.

4. Burger M, Catto JW, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, Kassouf W, Kiemeney LA, La Vecchia C, Shariat S, Lotan Y. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013 Feb;63(2):234-41. doi: 10.1016/j.eururo.2012.07.033. Epub 2012 Jul 25. PMID: 22877502.

5. Brennan P, Bogillot O, Cordier S, Greiser E, Schill W, Vineis P, Lopez-Abente G, Tzonou A, Chang-Claude J, Bolm-Audorff U, Jöckel KH, Donato F, Serra C, Wahrendorf J, Hours M, T'Mannetje A, Kogevinas M, Boffetta P. Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies. Int J Cancer. 2000 Apr 15;86(2):289-94. doi: 10.1002/(sici)1097-0215(20000415)86:2<289::aid-ijc21>3.0.co;2-m. PMID: 10738259.

6. Caini S, Del Riccio M, Vettori V, Francolini G, D'Ecclesiis O, Cai T, Gaeta A, Bonaccorsi G, Zanna I, Palli D, Gandini S. Prognostic Impact of Post-Diagnosis Smoking Cessation among Bladder Cancer Patients: A Systematic Literature Review and Meta-Analysis. Cancers (Basel). 2022 Aug 20;14(16):4022. doi: 10.3390/cancers14164022. PMID: 36011016; PMCID: PMC9406768.

7. Uroweb – MIBC Guidelines: https://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer

8. Burger M, Catto JW, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, Kassouf W, Kiemeney LA, La Vecchia C, Shariat S, Lotan Y. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013 Feb;63(2):234-41. doi: 10.1016/j.eururo.2012.07.033. Epub 2012 Jul 25. PMID: 22877502.

9. Weistenhofer W, Blaszkewicz M, Bolt HM, Golka K. N-acetyltransferase-2 and medical history in bladder cancer cases with a suspected occupational

disease (BK 1301) in Germany. J Toxicol Environ Health A. 2008;71(13-14):906-10. doi: 10.1080/15287390801988681. PMID: 18569594.

10. Chrouser K, Leibovich B, Bergstralh E, Zincke H, Blute M. Bladder cancer risk following primary and adjuvant external beam radiation for prostate cancer. J Urol. 2005 Jul;174(1):107-10; discussion 110-1. doi: 10.1097/01.ju.0000163459.57305.a1. PMID: 15947588.

11. Liu S, Yang T, Na R, Hu M, Zhang L, Fu Y, Jiang H, Ding Q. The impact of female gender on bladder cancer-specific death risk after radical cystectomy: a meta-analysis of 27,912 patients. Int Urol Nephrol. 2015 Jun;47(6):951-8. doi: 10.1007/s11255-015-0980-6. Epub 2015 Apr 19. PMID: 25894962.

12. Andreassen BK, Grimsrud TK, Haug ES. Bladder cancer survival: Women better off in the long run. Eur J Cancer. 2018 May;95:52-58. doi: 10.1016/j.ejca.2018.03.001. Epub 2018 Apr 7. PMID: 29635144.

13. Sørensen JB, Klee M, Palshof T, Hansen HH. Performance status assessment in cancer patients. An inter-observer variability study. Br J Cancer. 1993 Apr;67(4):773-5. doi: 10.1038/bjc.1993.140. PMID: 8471434; PMCID: PMC1968363.

14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83. doi: 10.1016/0021-9681(87)90171-8. PMID: 3558716.

15. Eva M. Wojcik, Daniel F.I. Kurtycz, Dorothy L. Rosenthal. (2022) *The Paris System for Reporting Urinary Cytology.* Cham: Springer. doi: 10.1007/978-3-030-88686-8.

16. Allison DB, VandenBussche CJ. Diagnostic challenges in urinary cytology: Practical insights from The Paris System for Reporting Urinary Cytology. Cancer Cytopathol. 2025 Aug;133(8):e70033. doi: 10.1002/cncy.70033. PMID: 40762622.

17. Linee guida AIOM – Tumori dell'urotelio, ed. 2024: https://www.aiom.it/linee-guida-aiom-2024-tumori-dellurotelio/

18. Choi SY, Yang YJ, Min KC, Lee YS, Choi J, Kim JH, Lee CU, Yang EJ, Tae JH. Diagnostic performance of narrow-band imaging and photodynamic diagnosis compared to white light cystoscopy for non-muscle invasive bladder cancer: A network meta-analysis of randomized trials. Investig Clin Urol. 2026

Mar;67(2):131-139. doi: 10.4111/icu.20250547. PMID: 41775443; PMCID: PMC12956772.

19. Compérat E, Amin MB, Berney DM, Cree I, Menon S, Moch H, Netto GJ, Rao V, Raspollini MR, Rubin MA, Srigley JR, Tan PH, Tickoo SK, Turajlic S, Tsuzuki T. What's new in WHO fifth edition - urinary tract. Histopathology. 2022 Oct;81(4):439-446. doi: 10.1111/his.14764. Epub 2022 Aug 16. PMID: 35942645.

20. Guo CC, Shen SS, Czerniak B. Recent Advances in the Classification of Bladder Cancer - Updates from the 5th Edition of the World Health Organization Classification of the Urinary and Male Genital Tumors. Bladder Cancer. 2023 Mar 31;9(1):1-14. doi: 10.3233/BLC-220106. PMID: 38994481; PMCID: PMC11181758.

21. James Brierley, Meredith Giuliani, Brian O'Sullivan, Brian Rous, Elizabeth Van Eycken. (2025) *TNM Classification of Malignant Tumours.* New Jersey: John Wiley & Sons Ltd.

22. Juste-Alvarez S, García-Rayo Encina C, Gómez Del Cañizo C, Hernandez-Arroyo M, Miranda-Utrera NR, Rodriguez-Antolin A, Guerrero-Ramos Félix F. Comparison of prognosis between primary and progressive muscle-invasive bladder carcinoma: A prospective analysis of long-term outcomes after radical cystectomy. Actas Urol Esp (Engl Ed). 2025 Oct;49(8):501815. English, Spanish. doi: 10.1016/j.acuroe.2025.501815. Epub 2025 Jul 9. PMID: 40645289.

23. Laert J, Lupi Manso N, França de Santana T, Santos PO. Pitfalls and Limitations of the Vesical Imaging-Reporting and Data System (VI-RADS): Challenges in the Multiparametric Magnetic Resonance Imaging (mpMRI) Assessment of Bladder Cancer. Cureus. 2025 Dec 14;17(12):e99197. doi: 10.7759/cureus.99197. PMID: 41541939; PMCID: PMC12800710.

24. Paik ML, Scolieri MJ, Brown SL, Spirnak JP, Resnick MI. Limitations of computerized tomography in staging invasive bladder cancer before radical cystectomy. J Urol. 2000 Jun;163(6):1693-6. PMID: 10799162.

25. Cowan NC, Turney BW, Taylor NJ, McCarthy CL, Crew JP. Multidetector computed tomography urography for diagnosing upper urinary tract urothelial tumour. BJU Int. 2007 Jun;99(6):1363-70. doi: 10.1111/j.1464-410X.2007.06766.x. Epub 2007 Apr 8. PMID: 17428251.

26. Lonati C, Mordasini L, Afferi L, De Cobelli O, Di Trapani E, Necchi A, Colombo R, Briganti A, Montorsi F, Simeone C, Zamboni S, Simone G, Karnes

RJ, Marra G, Soria F, Gontero P, Shariat SF, Pradere B, Hendricksen K, Ammiwala M, Rink M, Poyet C, Krajewski W, Baumeister P, Mattei A, Moschini M, Carando R; European Association of Urology - Young Academic Urologists (EAU-YAU): Urothelial Carcinoma Working Group. Diagnostic accuracy of preoperative lymph node staging of bladder cancer according to different lymph node locations: A multicenter cohort from the European Association of Urology - Young Academic Urologists. Urol Oncol. 2022 May;40(5):195.e27-195.e35. doi: 10.1016/j.urolonc.2022.01.002. Epub 2022 Feb 27. PMID: 35236621.

27. Fahmy O, Khairul-Asri MG, Schubert T, Renninger M, Stenzl A, Gakis G. Clinicopathological Features and Prognostic Value of Incidental Prostatic Adenocarcinoma in Radical Cystoprostatectomy Specimens: A Systematic Review and Meta-Analysis of 13,140 Patients. J Urol. 2017 Feb;197(2):385-390. doi: 10.1016/j.juro.2016.08.088. Epub 2016 Aug 26. PMID: 27569436.

28. Hernández V, Espinos EL, Dunn J, MacLennan S, Lam T, Yuan Y, Compérat E, Cowan NC, Gakis G, Lebrét T, van der Heijden AG, Witjes JA, Ribal MJ. Oncological and functional outcomes of sexual function-preserving cystectomy compared with standard radical cystectomy in men: A systematic review. Urol Oncol. 2017 Sep;35(9):539.e17-539.e29. doi: 10.1016/j.urolonc.2017.04.013. Epub 2017 May 8. PMID: 28495555.

29. Majdalany SE, Yaguchi G, Arora S, Ray C, Atiemo HO, Raza J. Genital Sparing Robot-Assisted Radical Cystectomy with Intracorporeal Neobladder & Paravaginal Repair. Urology. 2023 Sep;179:202-203. doi: 10.1016/j.urology.2023.05.031. Epub 2023 Jun 13. PMID: 37321278.

30. Djaladat H, Bruins HM, Miranda G, Cai J, Skinner EC, Daneshmand S. Reproductive organ involvement in female patients undergoing radical cystectomy for urothelial bladder cancer. J Urol. 2012 Dec;188(6):2134-8. doi: 10.1016/j.juro.2012.08.024. Epub 2012 Oct 18. PMID: 23083874.

31. Pacchetti A, Caviglia A, Lorusso V, Branger N, Maubon T, Rybikowski S, Perri D, Bozzini G, Pignot G, Walz J. Robot-assisted radical cystectomy with neobladder diversion in females: Safety profile and functional outcomes. Asian J Urol. 2024 Oct;11(4):618-624. doi: 10.1016/j.ajur.2024.02.008. Epub 2024 Feb 27. PMID: 39534011; PMCID: PMC11551516.

32. Simone G, Papalia R, Ferriero M, Guaglianone S, Castelli E, Collura D, Muto G, Gallucci M. Stage-specific impact of extended versus standard pelvic lymph node dissection in radical cystectomy. Int J Urol. 2013 Apr;20(4):390-7. doi: 10.1111/j.1442-2042.2012.03148.x. Epub 2012 Sep 12. PMID: 22970939.

33. Khetrapal P, Wong JKL, Tan WP, Rupasinghe T, Tan WS, Williams SB, Boorjian SA, Wijburg C, Parekh DJ, Wiklund P, Vasdev N, Khan MS, Guru KA, Catto JWF, Kelly JD. Robot-assisted Radical Cystectomy Versus Open Radical Cystectomy: A Systematic Review and Meta-analysis of Perioperative, Oncological, and Quality of Life Outcomes Using Randomized Controlled Trials. Eur Urol. 2023 Oct;84(4):393-405. doi: 10.1016/j.eururo.2023.04.004. Epub 2023 May 9. Erratum in: Eur Urol. 2023 Oct;84(4):e98-e99. doi: 10.1016/j.eururo.2023.06.023. PMID: 37169638.

34. Chan KG, Guru K, Wiklund P, Catto J, Yuh B, Novara G, Murphy DG, Al-Tartir T, Collins JW, Zhumkhawala A, Wilson TG; Pasadena Consensus Panel. Robot-assisted radical cystectomy and urinary diversion: technical recommendations from the Pasadena Consensus Panel. Eur Urol. 2015 Mar;67(3):423-31. doi: 10.1016/j.eururo.2014.12.027. Epub 2015 Jan 14. PMID: 25595099.

35. Collins JW, Tyritzis S, Nyberg T, Schumacher M, Laurin O, Khazaeli D, Adding C, Jonsson MN, Hosseini A, Wiklund NP. Robot-assisted radical cystectomy: description of an evolved approach to radical cystectomy. Eur Urol. 2013 Oct;64(4):654-63. doi: 10.1016/j.eururo.2013.05.020. Epub 2013 May 27. PMID: 23769588.

36. Mossanen M, Krasnow RE, Zlatev DV, Tan WS, Preston MA, Trinh QD, Kibel AS, Sonpavde G, Schrag D, Chung BI, Chang SL. Examining the relationship between complications and perioperative mortality following radical cystectomy: a population-based analysis. BJU Int. 2019 Jul;124(1):40-46. doi: 10.1111/bju.14636. Epub 2019 Apr 14. PMID: 30499636.

37. Sari Motlagh R, Mori K, Aydh A, Karakiewicz PI, Trinh QD, Shariat SF. Impact of hospital and surgeon volumes on short-term and long-term outcomes of radical cystectomy. Curr Opin Urol. 2020 Sep;30(5):701-710. doi: 10.1097/MOU.0000000000000805. PMID: 32732625.Hautmann RE, Herr HW, Pruthi RS, Aron M. Robotic radical cystectomy--is the diversion the Achilles' heel? J Urol. 2014 Dec;192(6):1601-3. doi: 10.1016/j.juro.2014.09.042. Epub 2014 Sep 20. PMID: 25245487.

38. Uroweb – NMIBC Guidelines: https://uroweb.org/guidelines/non-muscle-invasive-bladder-cancer/chapter/disease-management

39. Dal Moro F, Zattoni F, Tonet E, Morlacco A, Betto G, Novara G. Perioperative and Functional Results for Robot-assisted Radical Cystectomy with Totally Intracorporeal Neobladder in Male Patients via the Vesica Patavina (Ves.Pa.) Technique: IDEAL Stage 2a Report. Eur Urol Open Sci. 2023 Sep

22;57:8-15. doi: 10.1016/j.euros.2023.09.001. PMID: 37771917; PMCID: PMC10522971.

40. An, Sanghyun & Kim, Ik. (2021). Pelvic Anatomy for Distal Rectal Cancer Surgery. 10.5772/intechopen.99120.

41. Funaro, M.G., Bahlani, S. (2020). Anatomy of the Female Pelvis. In: Firoozi, F. (eds) Female Pelvic Surgery. Springer, Cham. https://doi.org/10.1007/978-3-030-28319-3_1

42. Lerner SP, Tangen C, Svatek RS, Daneshmand S, Pohar KS, Skinner E, Schuckman A, Sagalowsky AI, Smith ND, Kamat AM, Kassouf W, Plets M, Bangs R, Koppie TM, Alva A, La Rosa FG, Pal SK, Kibel AS, Canter DJ, Thompson IM Jr; SWOG S1011 Trial Investigators. Standard or Extended Lymphadenectomy for Muscle-Invasive Bladder Cancer. N Engl J Med. 2024 Oct 3;391(13):1206-1216. doi: 10.1056/NEJMoa2401497. Erratum in: N Engl J Med. 2026 Feb 12;394(7):728. doi: 10.1056/NEJMx240009. PMID: 39589370; PMCID: PMC11599768.

43. Korkes F, Fernandes E, Gushiken FA, Glina FPA, Baccaglini W, Timóteo F, Glina S. Bricker ileal conduit vs. Cutaneous ureterostomy after radical cystectomy for bladder cancer: a systematic review. Int Braz J Urol. 2022 Jan-Feb;48(1):18-30. doi: 10.1590/S1677-5538.IBJU.2020.0892. PMID: 33861058; PMCID: PMC8691241.

44. Roessler N, Miszczyk M, Miyajima K, Alfarhan AR, Alqahtani AS, Inoue S, Ofner H, Weiss J, Fazekas T, Ludwig TA, Vetterlein MW, Hemelrijck MV, Özdemir BC, Fisch M, Shariat SF. The Influence of Urinary Diversion Type on Body Image and Decision Regret Following Radical Cystectomy: A Systematic Review. Eur Urol Focus. 2025 Dec 12:S2405-4569(25)00355-4. doi: 10.1016/j.euf.2025.12.002. Epub ahead of print. PMID: 41390278.

45. Cicione A, De Nunzio C, Lombardo R, Trucchi A, Manno S, Lima E, Tubaro A. Complications and quality of life of ileal conduit, orthotopic neobladder and ureterocutaneostomy: systematic review of reports using the Clavien-Dindo Classification. Minerva Urol Nefrol. 2020 Aug;72(4):408-419. doi: 10.23736/S0393-2249.20.03641-3. PMID: 32734749.

46. Gu T, Chen T, Pan Y, Yu Q, Li J. Robot-assisted conversion of ureterocutaneous stoma to ileal conduit: a novel option for patients with post-cystectomy cutaneous diversion complicated by ureteral stricture and recurrent infections. Front Urol. 2025 Aug 15;5:1634602. doi: 10.3389/fruro.2025.1634602. PMID: 40895648; PMCID: PMC12394047.

47. Lenis AT, Lec PM, Chamie K, Mshs MD. Bladder Cancer: A Review. JAMA. 2020 Nov 17;324(19):1980-1991. doi: 10.1001/jama.2020.17598. PMID: 33201207.

48. Hautmann RE. Surgery illustrated - surgical atlas ileal neobladder. BJU Int. 2010 Apr;105(7):1024-35. doi: 10.1111/j.1464-410X.2010.09283.x. PMID: 20356328.

49. Goh AC, Gill IS, Lee DJ, de Castro Abreu AL, Fairey AS, Leslie S, Berger AK, Daneshmand S, Sotelo R, Gill KS, Xie HW, Chu LY, Aron M, Desai MM. Robotic intracorporeal orthotopic ileal neobladder: replicating open surgical principles. Eur Urol. 2012 Nov;62(5):891-901. doi: 10.1016/j.eururo.2012.07.052. Epub 2012 Aug 17. PMID: 22920581.

50. Lavallée E, Wiklund P. The Studer Neobladder: An Established and Reproducible Technique for Intracorporeal Urinary Diversion. Eur Urol Open Sci. 2021 Nov 24;35:18-20. doi: 10.1016/j.euros.2021.09.019. PMID: 34888533; PMCID: PMC8637466.

51. Tappero S, Dell'Oglio P, Cerruto MA, Sanchez Salas R, Buisan Rueda O, Simone G, Hendricksen K, Soria F, Umari P, Antonelli A, Briganti A, Montorsi F, de Cobelli O, Terrone C, Galfano A, Moschini M, Di Trapani E; European Association of Urology-Young Academic Urologists EAU-YAU: Urothelial Carcinoma Working Group. Ileal Conduit Versus Orthotopic Neobladder Urinary Diversion in Robot-assisted Radical Cystectomy: Results from a Multi-institutional Series. Eur Urol Open Sci. 2023 Feb 18;50:47-56. doi: 10.1016/j.euros.2023.01.009. PMID: 37101775; PMCID: PMC10123439.

52. Dal Moro F, Zattoni F. Ves.Pa.-Designing a Novel Robotic Intracorporeal Orthotopic Ileal Neobladder. Urology. 2016 May;91:99-103. doi: 10.1016/j.urology.2016.02.008. Epub 2016 Feb 18. PMID: 26905031.

53. Studer UE, Ackermann D, Casanova GA, Zingg EJ. Three years' experience with an ileal low pressure bladder substitute. Br J Urol. 1989 Jan;63(1):43-52. doi: 10.1111/j.1464-410x.1989.tb05122.x. PMID: 2920259.

54. Piramide F, Turri F, Amparore D, Fallara G, De Groote R, Knipper S, Wuernschimmel C, Bravi CA, Lambert E, Di Maida F, Liakos N, Pellegrino F, Andras I, Mastrorosa A, Tillu N, Mastroianni R, Paciotti M, Wenzel M, Bianchi R, di Trapani E, Moschovas MC, Gandaglia G, Moschini M, D'Hondt F, Rocco

B, Fiori C, Galfano A, Minervini A, Simone G, Briganti A, De Cobelli O, Gaston R, Montorsi F, Breda A, Wiklund P, Porpiglia F, Mottrie A, Larcher A, Dell'Oglio P; Junior ERUS/YAU Working Group on Robot-assisted Surgery of the European Association of Urology. Atlas of Intracorporeal Orthotopic Neobladder Techniques After Robot-assisted Radical Cystectomy and Systematic Review of Clinical Outcomes. Eur Urol. 2024 Apr;85(4):348-360. doi: 10.1016/j.eururo.2023.11.017. Epub 2023 Dec 2. PMID: 38044179.

55. Lavallée E, Wiklund P. The Studer Neobladder: An Established and Reproducible Technique for Intracorporeal Urinary Diversion. Eur Urol Open Sci. 2021 Nov 24;35:18-20. doi: 10.1016/j.euros.2021.09.019. PMID: 34888533; PMCID: PMC8637466.

56. Elsandoby O, Masoud M, Darlington D, Siddarth M, Motiwala Z, Chang T, Motiwala H, Massanova M. Robot-Assisted Radical Cystectomy (RARC) and Intracorporeal Studer Neobladder: Surgical Technique, Feasibility, and Early Functional and Oncological Outcomes. Cureus. 2025 Aug 17;17(8):e90294. doi: 10.7759/cureus.90294. PMID: 40964551; PMCID: PMC12439744.

57. Martini A, Falagario UG, Russo A, Mertens LS, Di Gianfrancesco L, Bravi CA, Vollemaere J, Abdeen M, Mendrek M, Kjøbli E, Buse S, Wijburg C, Touzani A, Ploussard G, Antonelli A, Schwenk L, Ebbing J, Vasdev N, Froelicher G, John H, Canda AE, Balbay MD, Stoll M, Edeling S, Witt JH, Leyh-Bannurah SR, Siemer S, Stoeckle M, Mottrie A, D'Hondt F, Crestani A, Porreca A, van der Poel H, Decaestecker K, Gaston R, Peter Wiklund N, Hosseini A; Scientific Working Group of the Robotic Urology Section of the European Association of Urology. Robot-assisted Radical Cystectomy with Orthotopic Neobladder Reconstruction: Techniques and Functional Outcomes in Males. Eur Urol. 2023 Nov;84(5):484-490. doi: 10.1016/j.eururo.2023.04.009. Epub 2023 Apr 26. PMID: 37117109.

58. Hussein AA, Ahmed YE, Kozlowski JD, May PR, Nyquist J, Sexton S, Curtin L, Peabody JO, Abol-Enein H, Guru KA. Robot-assisted approach to 'W'-configuration urinary diversion: a step-by-step technique. BJU Int. 2017 Jul;120(1):152-157. doi: 10.1111/bju.13824. Epub 2017 Mar 22. PMID: 28220593.

59. Hautmann RE, Volkmer B, Egghart G, Frohneberg D, Gottfried HW, Gschwend J, Hefty R, Kleinschmidt K, Küfer R, Miller K, de Petriconi R, Simon J, Wenderoth U. Functional Outcome and Complications following Ileal Neobladder Reconstruction in Male Patients without Tumor Recurrence. More than 35 Years of Experience from a Single Center. J Urol. 2021 Jan;205(1):174-

182. doi: 10.1097/JU.0000000000001345. Epub 2020 Aug 28. PMID: 32856988.

60. Fontana D, Bellina M, Fasolis G, Frea B, Scarpa RM, Mari M, Rolle L, Destefanis P. Y-neobladder: an easy, fast, and reliable procedure. Urology. 2004 Apr;63(4):699-703. doi: 10.1016/j.urology.2003.11.015. PMID: 15072884.

61. Mao W, Chen S, Zhang L, Li T, Sun S, Xu B, Zhu W, Zhang G, Zhang L, Wu J, Chen M. Robot-Assisted Laparoscopic Radical Cystectomy and Modified Y-Shaped Ileal Orthotopic Neobladder Reconstruction. Front Surg. 2022 Jun 1;9:889536. doi: 10.3389/fsurg.2022.889536. PMID: 35722533; PMCID: PMC9198462.

62. Anceschi U, Basile S, Amparore D, Di Maida F, Mastroianni R, De Cillis S, D'Ippolito G, Grosso AA, Tuderti G, Rosato E, Flammia RS, Lambertini L, Brassetti A, Conte FL, Finazzi Agrò E, Fiori C, Porpiglia F, Minervini A, Simone G. "Far beyond the shape": an early head-to-head comparative urodynamic analysis of three contemporary totally intracorporeal robotic orthotopic neobladder techniques. J Robot Surg. 2025 Oct 14;19(1):689. doi: 10.1007/s11701-025-02821-4. PMID: 41085766.

63. Minervini A, Vanacore D, Vittori G, Milanesi M, Tuccio A, Siena G, Campi R, Mari A, Gavazzi A, Carini M. Florence robotic intracorporeal neobladder (FloRIN): a new reconfiguration strategy developed following the IDEAL guidelines. BJU Int. 2018 Feb;121(2):313-317. doi: 10.1111/bju.14077. Epub 2017 Dec 11. PMID: 29140596.

64. Minervini A, Di Maida F, Tasso G, Mari A, Bossa R, Sforza S, Grosso AA, Tellini R, Vittori G, Siena G, Tuccio A, Masieri L, Carini M. Robot assisted radical cystectomy with Florence robotic intracorporeal neobladder (FloRIN): Analysis of survival and functional outcomes after first 100 consecutive patients upon accomplishment of phase 3 IDEAL framework. Eur J Surg Oncol. 2021 Oct;47(10):2651-2657. doi: 10.1016/j.ejso.2021.05.007. Epub 2021 May 15. PMID: 34023169.

65. Yu HY, Hevelone ND, Lipsitz SR, Kowalczyk KJ, Nguyen PL, Choueiri TK, Kibel AS, Hu JC. Comparative analysis of outcomes and costs following open radical cystectomy versus robot-assisted laparoscopic radical cystectomy: results from the US Nationwide Inpatient Sample. Eur Urol. 2012 Jun;61(6):1239-44. doi: 10.1016/j.eururo.2012.03.032. Epub 2012 Mar 30. PMID: 22482778.

66. Novara G, Catto JW, Wilson T, Annerstedt M, Chan K, Murphy DG, Motttrie A, Peabody JO, Skinner EC, Wiklund PN, Guru KA, Yuh B. Systematic review and cumulative analysis of perioperative outcomes and complications after robot-assisted radical cystectomy. Eur Urol. 2015 Mar;67(3):376-401. doi: 10.1016/j.eururo.2014.12.007. Epub 2015 Jan 2. PMID: 25560798.

67. Shabsigh A, Korets R, Vora KC, Brooks CM, Cronin AM, Savage C, Raj G, Bochner BH, Dalbagni G, Herr HW, Donat SM. Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. Eur Urol. 2009 Jan;55(1):164-74. doi: 10.1016/j.eururo.2008.07.031. Epub 2008 Jul 18. PMID: 18675501.

68. Parekh DJ, Reis IM, Castle EP, Gonzalgo ML, Woods ME, Svatek RS, Weizer AZ, Konety BR, Tollefson M, Krupski TL, Smith ND, Shabsigh A, Barocas DA, Quek ML, Dash A, Kibel AS, Shemanski L, Pruthi RS, Montgomery JS, Weight CJ, Sharp DS, Chang SS, Cookson MS, Gupta GN, Gorbonos A, Uchio EM, Skinner E, Venkatramani V, Soodana-Prakash N, Kendrick K, Smith JA Jr, Thompson IM. Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label, randomised, phase 3, non-inferiority trial. Lancet. 2018 Jun 23;391(10139):2525-2536. doi: 10.1016/S0140-6736(18)30996-6. PMID: 29976469.

69. Venkatramani V, Reis IM, Castle EP, Gonzalgo ML, Woods ME, Svatek RS, Weizer AZ, Konety BR, Tollefson M, Krupski TL, Smith ND, Shabsigh A, Barocas DA, Quek ML, Dash A, Kibel AS, Pruthi RS, Montgomery JS, Weight CJ, Sharp DS, Chang SS, Cookson MS, Gupta GN, Gorbonos A, Uchio EM, Skinner E, Soodana-Prakash N, Becerra MF, Swain S, Kendrick K, Smith JA Jr, Thompson IM, Parekh DJ. Predictors of Recurrence, and Progression-Free and Overall Survival following Open versus Robotic Radical Cystectomy: Analysis from the RAZOR Trial with a 3-Year Followup. J Urol. 2020 Mar;203(3):522-529. doi: 10.1097/JU.0000000000000565. Epub 2019 Sep 24. PMID: 31549935; PMCID: PMC7487279.

70. von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, Bodrogi I, Albers P, Knuth A, Lippert CM, Kerbrat P, Sanchez Rovira P, Wersall P, Cleall SP, Roychowdhury DF, Tomlin I, Visseren-Grul CM, Conte PF. Gemcitabine and Cisplatin Versus Methotrexate, Vinblastine, Doxorubicin, and Cisplatin in Advanced or Metastatic Bladder Cancer: Results of a Large, Randomized, Multinational, Multicenter, Phase III Study. J Clin Oncol. 2023 Aug 10;41(23):3881-3890. doi: 10.1200/JCO.22.02763. PMID: 37549482.

71. Galsky MD, Hahn NM, Rosenberg J, Sonpavde G, Hutson T, Oh WK, Dreicer R, Vogelzang N, Sternberg CN, Bajorin DF, Bellmunt J. Treatment of patients with metastatic urothelial cancer "unfit" for Cisplatin-based chemotherapy. J Clin Oncol. 2011 Jun 10;29(17):2432-8. doi: 10.1200/JCO.2011.34.8433. Epub 2011 May 9. PMID: 21555688.

72. Yin M, Joshi M, Meijer RP, Glantz M, Holder S, Harvey HA, Kaag M, Fransen van de Putte EE, Horenblas S, Drabick JJ. Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer: A Systematic Review and Two-Step Meta-Analysis. Oncologist. 2016 Jun;21(6):708-15. doi: 10.1634/theoncologist.2015-0440. Epub 2016 Apr 6. PMID: 27053504; PMCID: PMC4912364.

73. Pietzak EJ, Zabor EC, Bagrodia A, Armenia J, Hu W, Zehir A, Funt S, Audenet F, Barron D, Maamouri N, Li Q, Teo MY, Arcila ME, Berger MF, Schultz N, Dalbagni G, Herr HW, Bajorin DF, Rosenberg JE, Al-Ahmadie H, Bochner BH, Solit DB, Iyer G. Genomic Differences Between "Primary" and "Secondary" Muscle-invasive Bladder Cancer as a Basis for Disparate Outcomes to Cisplatin-based Neoadjuvant Chemotherapy. Eur Urol. 2019 Feb;75(2):231-239. doi: 10.1016/j.eururo.2018.09.002. Epub 2018 Oct 2. PMID: 30290956; PMCID: PMC6339572.

74. Arora A, Zugail AS, Pugliesi F, Cathelineau X, Macek P, Barbé Y, Karnes RJ, Ahmed M, Di Trapani E, Soria F, Alvarez-Maestro M, Montorsi F, Briganti A, Necchi A, Pradere B, D'Andrea D, Krajewski W, Roumiguié M, Bajeot AS, Hurle R, Contieri R, Carando R, Teoh JY, Roupret M, Benamran D, Ploussard G, Mir MC, Sanchez-Salas R, Moschini M. Neoadjuvant chemotherapy does not increase peri-operative morbidity following radical cystectomy. World J Urol. 2022 Jul;40(7):1697-1705. doi: 10.1007/s00345-022-04012-4. Epub 2022 Apr 30. PMID: 35488914.

75. Advanced Bladder Cancer (ABC) Meta-analysis Collaborators Group. Adjuvant Chemotherapy for Muscle-invasive Bladder Cancer: A Systematic Review and Meta-analysis of Individual Participant Data from Randomised Controlled Trials. Eur Urol. 2022 Jan;81(1):50-61. doi: 10.1016/j.eururo.2021.09.028. Epub 2021 Nov 19. PMID: 34802798; PMCID: PMC8708165.

76. Galsky MD, Stensland KD, Moshier E, Sfakianos JP, McBride RB, Tsao CK, Casey M, Boffetta P, Oh WK, Mazumdar M, Wisnivesky JP. Effectiveness of Adjuvant Chemotherapy for Locally Advanced Bladder Cancer. J Clin Oncol. 2016 Mar 10;34(8):825-32. doi: 10.1200/JCO.2015.64.1076. Epub 2016 Jan 19. PMID: 26786930.

77. Sternberg CN, Skoneczna I, Kerst JM, Albers P, Fossa SD, Agerbaek M, Dumez H, de Santis M, Théodore C, Leahy MG, Chester JD, Verbaeys A, Daugaard G, Wood L, Witjes JA, de Wit R, Geoffrois L, Sengelov L, Thalmann G, Charpentier D, Rolland F, Mignot L, Sundar S, Symonds P, Graham J, Joly F, Marreaud S, Collette L, Sylvester R; European Organisation for Research and Treatment of Cancer Genito-Urinary Cancers Group; Groupe d'Etude des Tumeurs Urogénitales; National Cancer Research Institute Bladder Cancer Study Group; National Cancer Institute of Canada Clinical Trials Group; German Association of Urologic Oncology. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. Lancet Oncol. 2015 Jan;16(1):76-86. doi: 10.1016/S1470-2045(14)71160-X. Epub 2014 Dec 11. PMID: 25498218.

78. Wei SC, Duffy CR, Allison JP. Fundamental Mechanisms of Immune Checkpoint Blockade Therapy. Cancer Discov. 2018 Sep;8(9):1069-1086. doi: 10.1158/2159-8290.CD-18-0367. Epub 2018 Aug 16. PMID: 30115704.

79. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, Vogelzang NJ, Climent MA, Petrylak DP, Choueiri TK, Necchi A, Gerritsen W, Gurney H, Quinn DI, Culine S, Sternberg CN, Mai Y, Poehlein CH, Perini RF, Bajorin DF; KEYNOTE-045 Investigators. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med. 2017 Mar 16;376(11):1015-1026. doi: 10.1056/NEJMoa1613683. Epub 2017 Feb 17. PMID: 28212060; PMCID: PMC5635424.

80. Powles T, Csőszi T, Özgüroğlu M, Matsubara N, Géczi L, Cheng SY, Fradet Y, Oudard S, Vulsteke C, Morales Barrera R, Fléchon A, Gunduz S, Loriot Y, Rodriguez-Vida A, Mamtani R, Yu EY, Nam K, Imai K, Homet Moreno B, Alva A; KEYNOTE-361 Investigators. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. Lancet Oncol. 2021 Jul;22(7):931-945. doi: 10.1016/S1470-2045(21)00152-2. Epub 2021 May 26. PMID: 34051178.

81. Grivas P, Park SH, Voog E, Caserta C, Gurney H, Bellmunt J, Kalofonos H, Ullén A, Loriot Y, Sridhar SS, Yamamoto Y, Petrylak DP, Sternberg CN, Gupta S, Huang B, Costa N, Laliberte RJ, di Pietro A, Valderrama BP, Powles T. Avelumab First-line Maintenance Therapy for Advanced Urothelial Carcinoma: Comprehensive Clinical Subgroup Analyses from the JAVELIN Bladder 100 Phase 3 Trial. Eur Urol. 2023 Jul;84(1):95-108. doi: 10.1016/j.eururo.2023.03.030. Epub 2023 Apr 28. PMID: 37121850.

82. Nikanjam M, Pérez-Granado J, Gramling M, Larvol B, Kurzrock R. Nectin-4 expression patterns and therapeutics in oncology. Cancer Lett. 2025 Jul 10;622:217681. doi: 10.1016/j.canlet.2025.217681. Epub 2025 Apr 8. PMID: 40209851; PMCID: PMC12132789.

83. European Union Register of Medicinal Products: https://ec.europa.eu/health/documents/community-register/2024/20240927163720/anx_163720_it.pdf

84. Powles TB, Van der Heijden MS, Loriot Y, Bedke J, Valderrama BP, Iyer G, Kikuchi E, Hoffman-Censits J, Vulsteke C, Drakaki A, Rausch S, Arafat W, Park SH, Swami U, Li JR, Duran I, Gorla S, Homet Moreno B, Yu X, Lu YT, Gupta S. Enfortumab vedotin plus pembrolizumab in untreated locally advanced or metastatic urothelial carcinoma: 2.5-year median follow-up of the phase III EV-302/KEYNOTE-A39 trial. Ann Oncol. 2025 Oct;36(10):1212-1219. doi: 10.1016/j.annonc.2025.05.536. Epub 2025 Jun 1. PMID: 40460988.

85. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004 Aug;240(2):205-13. doi: 10.1097/01.sla.0000133083.54934.ae. PMID: 15273542; PMCID: PMC1360123.

86. Barry MJ, Fowler FJ, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al. The American Urological Association Symptom Index for Benign Prostatic Hyperplasia. Journal of Urology [Internet]. 1992 Nov 1;148(5 Part 1):1549–57. Available from: https://doi.org/10.1016/S0022-5347(17)36966-5

87. Avery K, Donovan J, Peters TJ, Shaw C, Gotoh M, Abrams P. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. Neurourol Urodyn. 2004;23(4):322-30. doi: 10.1002/nau.20041. PMID: 15227649.

88. Johar RS, Hayn MH, Stegemann AP, Ahmed K, Agarwal P, Balbay MD, Hemal A, Kibel AS, Muhletaler F, Nepple K, Pattaras JG, Peabody JO, Palou Redorta J, Rha KH, Richstone L, Saar M, Schanne F, Scherr DS, Siemer S, Stökle M, Weizer A, Wiklund P, Wilson T, Woods M, Yuh B, Guru KA. Complications after robot-assisted radical cystectomy: results from the International Robotic Cystectomy Consortium. Eur Urol. 2013 Jul;64(1):52-7. doi: 10.1016/j.eururo.2013.01.010. Epub 2013 Jan 16. PMID: 23380164.