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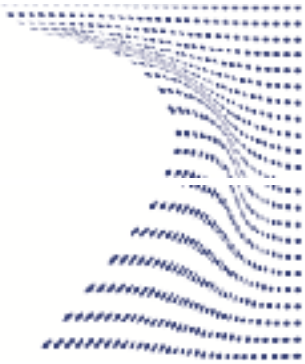

Doctoral Program in bioengineering and medical-surgical science

The role of the cystectomy and minimally invasive surgery in the complex patient with bladder cancer

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Summary

Radical cystectomy (RC) is currently the gold standard treatment option for muscle invasive bladder cancer (MIBC) due to its undisputable oncological efficacy. Despite advances in surgical techniques and postoperative care, the procedure is associated with significant morbidity. Recent series adopting a standardized methodology for reporting of complications observed that half of patients experienced at least a single complication within 3 months after surgery which was categorized as severe in 15% and lethal in 3% of cases. Apart from the overall morbidity rate related to this procedure, there are subgroups of patients in which RC could be characterized by higher complication and mortality rates.

The majority of the candidates to this surgery are older than 75 yrs and with a consistent oncological history, frequently including radiation treatment of pelvic organs. According to the available literature, age, comorbidities and previous history of radiation of the pelvis could represent limiting factors to this surgery. In these patients with a very high risk of surgical complications and peri-operative mortality, the oncological advantages deriving from cystectomy still represent an open debate. By the way, at the current state of knowledge, RC still represents the only curative treatment option especially in those patients with previous history of pelvic radiation.

Apart from all these considerations, the real impact of prior radiation and age on the morbidity after RC remains controversial in the literature, with conflicting results even in the most recent series.

Our research activity aims to clarify complication and perioperative mortality rates in these subgroups of complex patients that require RC.

Contents

Introduction

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Apart from all these considerations, the real impact of prior radiation and age on the morbidity after RC remains controversial in the literature, with conflicting results even in the most recent series.

Our research activity aims to clarify complication and perioperative mortality rates in these subgroups of complex patients that require RC. Moreover we tried to evaluate the possible role of minimally invasive surgery (robotic cystectomy) in order to reduce intra and post operative complications.

Narrative section

1.1 Epidemiology of bladder cancer

Bladder cancer is one of the tumors most frequently diagnosed by the urologist. The annual incidence of this neoplasm is about 4.5 times higher in men than in women. The majority of cases occur in people aged over 60.

Between 1984 and 1993 the incidence of bladder cancer in the United States increased by 36%, and most of them were males. This gender discrepancy remains particularly striking, because over the past 30 years women have shared with men workplace and have changed habits that exposed them to both occupational and environmental carcinogens (such as cigarette smoke) from whose exposure they were previously protected. The explanation for this seemingly incomprehensible trend can be found in genetic, hormonal, anatomical factors (e.g. urinary retention at which elderly men are subject to the related obstruction caused by prostatic hypertrophy).

The incidence of bladder cancer would seem to be conditioned by race: 2 times more frequent among white males than black ones and 1.5 times more frequent among white women than black ones. The reason for this difference is unclear, but recent evidence suggests that the greatest risk that distinguishes white subjects is mainly limited to non-invasive forms, implying a diagnostic delay in black subjects. In most cases the tumor starts in the middle or advanced age: the average age of presentation is 69 years for men and 71 years for women. Cancer mortality is also higher in the elderly. In adolescents and young adults under the age of 30, bladder cancer is very rare, tends to express a well differentiated histology and behaves in a less aggressive way. Younger patients appear to have a more favorable prognosis because of the prevalence of low-grade surface forms; however the risk of progression of the disease is the same in young and elderly patients.

1.2 Aetiology and risk factors

The most important risk factors are exposure to different chemicals, cigarette smoking, chronic infectious cystitis, the chronic presence of bladder stones and treatment with cyclophosphamide.

The aniline dyes, introduced in the late nineteenth century to colour the tissues, are urothelial carcinogens. Several other chemical compounds have been identified for their carcinogenic potential: 2-naphthylamine, 4-aminodiphenyl, 4-nitrodiphenyl, 4,4-diaminodiphenyl (benzidine) and 2-amino-1-naphthol, the combustion gases and coal ash.

Smokers have a 4 times higher incidence of bladder cancer than non-smokers. The risk is related to the number of cigarettes smoked, the number of years and the degree of inhalation. This has been observed in both genders. Ex-smokers present a partially lower risk than smokers: smoking cessation, in fact, gradually reduces the risk of getting sick, but over a period of 20 years. The chemical in cigarette smoke specifically responsible for the tumour has not been identified yet.

Chronic cystitis, the presence of indwelling catheters or endovesical stones, can induce the development of a specific tumor histotype, squamous cell carcinoma. Moreover, chronic schistosoma haematobium cystitis (parasitic infestation of endemic spread in Egypt, also called bilharziosis) increases the risk of developing squamous carcinoma.

Several studies have evaluated the possible contribution of the human papillomavirus (HPV) in the tumor development, with widely divergent results. Its role in carcinogenesis bladder remains therefore uncertain.

Patients receiving cyclophosphamide treatment have an increased risk (up to 9 times) to develop bladder cancer. A metabolite of cyclophosphamide, acrolein, is believed to be responsible for both hemorrhagic cystitis and bladder cancer. However, the

appearance of cystitis does not necessarily correlate with tumor development. The latency period is relatively short (6-13 years) and most of these neoplasms are muscle invasive at the time of diagnosis. Several authors recommend taking aggressive therapy immediately after diagnosis, even if the tumor is not invasive, considering the high rate of progression observed in patients in whom cystectomy is delayed. There is no evidence confirming heredity in bladder cancer, although family groupings of this disease have been described. Lynch et al. (1987) also noted an increased risk of developing the tumor in the relatives of 49 patients affected by Lynch II syndrome[15]. However, this was a fairly heterogeneous risk, since only 3 families out of 49 showed a really high level of risk. The authors, however, do not report whether the family members in question were also smokers. It is an omission important, since it is shown that the increase in family risk affects mainly smokers.

1.3 Natural history of the disease

Transitional cell carcinoma represents a widespread disease, which originates from the urothelial mucosa. This suggests the hypothesis of a polyclonal etiology, also supported by the fact that relapses can develop many years after resection of the primary tumor. In support of the hypothesis of polyclonal origin, immunohistochemical and immunocytochemical studies have shown that the histologically and cystoscopically normal-looking urothelium, located at a distance from the neoplastic masses, shares with them the altered expression of tumor indices such as G-actin or the EGF receptor. According to another hypothesis, in some cases multiple tumors derive from a single cell clone, which has spread to other sites of the urinary tract through implantation, transepithelial migration or lymphatic / vascular diffusion. About 5% of patients with superficial papillary neoplasms and approximately 20% of patients with high grade lesions (including the CIS) have vascular or lymphatic metastases.

In American population, 55-60% of newly diagnosed bladder tumors corresponds to a superficial transitional cell papillary carcinoma, with a moderate or good differentiation. Most of these patients develop one o more recurrences after endoscopic resection, these relapses usually reflect the initial neoplastic characteristics. Unfortunately, up to a quarter of cases presents a high-grade recurrence and 10% of patients develop subsequently invasive and metastatic cancer. 40-45% of newly diagnosed bladder carcinomas have high-grade lesions, e more than half of them are muscle infiltrating forms.

2. Radiation therapy

2.1 Physical characteristics of radiation therapy

Radiation is electromagnetic waves characterized by a wavelength λ and by a frequency ν ($\lambda\nu = c$, speed of light, equal to 300000 km / s). Since the wavelength and frequency of a radiation are inversely proportional, the shorter the wavelength, the greater the frequency, and hence its energy ($E = h\nu$). Among all the electromagnetic spectrum, human eye can only perceive wavelengths between 400 and 700 nm (visible light). Ionizing radiation has a higher frequency than visible light and, having more energy. These radiations can ionize atoms (or molecules) and consequently and, consequently, to make changes to the biological tissues they pass through, causing the modification and / or destruction of DNA chains within cells[1]. The understanding of these effects has made it possible to use elementary particles and ionizing radiation profitably both in nuclear medicine as tracers and in radiation therapy as an essential factor in the fight against cancer. The main goal of radiation therapy is local tumor control (locoregional radiation therapy). To achieve this, the tumor tissue must absorb a dose of radiation high enough to destroy it. Unfortunately, a part of the radiation reaches the surrounding healthy tissues, with a consequently risk of complications and / or serious damage, even irreversible[2]. The ideal situation is to deposit a large amount of energy in the tumor volume, saving the surrounding healthy tissues in order to avoid the lateral diffusion of the beam, both obtaining a well-defined

distribution of the energy only in the target area. The way of transferring energy from radiation to the fabric is expressed in LET (Linear Energy Transfer) which is the density of energy transferred along the path of the individual particles and it is proportional to their energy and mass. In addition to the dose absorbed, the treatment of a tumor is also influenced by other parameters such as radiosensitivity and the scheme adopted for dose fractionation.

2.2 How to prepare the patient to the radiation treatment.

Radiation treatment is a process in which the patient is at the center of interest and the procedures adopted are customized according to the treatment plan[17]. The realization starts with the clinical characterization of the patient, during which the site and anatomical relationships of the neoplasm, the target volume, the total dose, the dose per fraction and the dose to the critical organs are assessed[17]. The complexity of the treatment plan depends on the purpose of the treatment itself, palliative or curative. This step is important to decide the optimal radiotherapy technique in order to deliver a homogeneous dose and minimize the dose absorbed by the surrounding healthy tissues. The identification of the target volume is assessed by staging procedures (CT, MRI, PET and CT-PET, scintigraphy, etc.) and by the histological examination obtained from biopsies or surgery. The practical identification of the target volume is achieved through the simulator or through the use of the TC. This phase is preceded by the choice of positioning, a fundamental step for the daily reproducibility of irradiation. The systematic use of three-dimensional images produced by CT in planning and in the personalization of the treatment plan, together with the use of dedicated software, made possible a virtual simulation of the volumes to be irradiated. In calculating the dose distribution within the volumes of interest, it is necessary to consider the ICRU 50 (International Commission on Radiation Units and Measurements Report 50) recommendations[18]. "ICRU 50" identifies some volumes of interest: the GTV (Gross Tumor Volume) or macroscopic tumor volume,

is the volume that contains the site and extent of the documented neoplasm; the CTV (Clinical Target Volume) or clinical target volume, includes the GTV and the surrounding areas where the microscopic disease is likely to be present; the PTV (Planning Target Volume) or planned target volume, includes the CTV with adequate margins related to the geometry of the radiation and the possible uncertainties of the positioning (Set-up Margin, SM) and the movements of the internal organs (Internal Margin, IM)[19,20].

2.3 Effects of radiation on tumour and normal tissue

The electromagnetic radiation commonly used in radiotherapy (X-rays) are indirectly ionizing because, after being absorbed by the biological tissue they pass through, they release their energy to charged particles (electrons) which will be responsible for real start of biological damage. Charged particles can have a direct action of damage on the target tissue or have an indirect action of damage through the production of free radicals which will cause injury, acting at the level of the double helix DNA and creating important biological effects. When DNA damage occurs, the complex enzyme mechanism for repairing radio-induced damage mediated by multiple genes is activated immediately, including the tumor suppressor gene p53. This process can lead to a complete repair of the damage, resulting in the formation of chromosomal aberrations or chromatid aberrations.

The cell is more radiosensitive when it is irradiated in the G1-S and G2-M phase of the cell cycle, while is more radioresistant when irradiated in phase S (DNA synthesis) or in G0. Unrepaired damage to the DNA induces various effects of lethality or cell sublethality depending on the histotype: the apoptotic death process is frequent in lymphocytes and male germ cells; the epithelial cells frequently undergo cellular necrosis processes; connective tissue cells undergo mitotic catastrophe (they

remain alive for a long time without replicating and die when they activate mitosis); other cells no longer replicate by remaining in mitotic arrest.

In healthy tissues, radio induced cell death leads to acute or subacute effects (damage epithelium, hematopoietic system etc) and late effects (damage to endothelial cells and to fibroblasts). The resolution of acute and subacute toxicities occurs through processes of cellular recruitment (from phase G0 to G1) and accelerated restocking (activation of the stamina cells). If some somatic cells manage to survive after irradiation with a DNA not completely repaired, slow malignant transformation processes can be activated, leading to the appearance of a radio-induced tumor. If the surviving cell with altered DNA is a germ cell, biological effects may express themselves through foetal malformations or induction of tumors in adolescence. In tumor tissues, cell death by apoptosis or necrosis leads to sterilization of tumor clones with consequent potential eradication of the malignant tumor (tumor radiosensitivity). If cancer cells trigger a complete repair process, the cell can survive the action of radiation and maintain its proliferative state (tumour radio-resistance). The rationale for radiation therapy in cancer patients is to induce damage to healthy tissue cells and tumour tissues and to exploit them different capacities to repair DNA induced damage in healthy cells (good shelter and survival) and in cancer cells (bad shelter and cell death). This difference promotes the treatment of patients with tumours with good or intermediate intrinsic radiosensitivity (lymphomas, seminomas of the testicle, squamous cell tumours, adenocarcinomas). Other tumors are difficult to treat with radiotherapy as they have low intrinsic radiosensitivity (soft tissue and bone sarcomas, glial tumors, melanomas)[23].

Experimental Section

1 Cystectomy in irradiated patients

1.1 Materials and methods

The study was performed as a multi-centric retrospective data collection at 28 high-volume radical cystectomy (RC) centers (defined as>30 procedures per year).

1.1.1 Inclusion criteria

Patients treated with cystectomy following previous radiation (pRTC) were eligible for the study. This included any urological, hematological, gynecological or gastrointestinal malignancy or medical conditions that resulted in radiotherapy (RT) to the abdomen, pelvis or perineum prior to cystectomy. Availability of information on complications and clinical outcome for up to a minimum of 1 year after cystectomy was required. Patients undergoing cystectomy between 1983 and the end of 2015 were eligible.

1.1.2 Assessment of surgical outcomes

Outcomes of pRTC were reported according to the EAU guidelines panel recommendations for reporting and grading of complications after urological procedures[24]. Complications were categorized according to the type (medical and surgical) and the time of onset (early, within 30 days; intermediate, between 30 and 90 days; and late, occurring after 90 days). Any complication was graded according to the Clavien–Dindo classification [25]. Minor complications were defined as grade 1 and 2, and major complications as grade 3–5.

1.1.3 Statistical analysis

The differences in continuous variables were analyzed using the Mann–Whitney U test (two categories) and the Kruskal–Wallis test (three or more categories). Associations between categorical variables were assessed using the Fisher's exact and 2-test. Uni- and multivariable logistic regression models assessed the risk of variable parameters with any complication and any major complication, respectively. Multivariable regression analyses were carried out to adjust for the number of the prognostic factors using the most important variables that had been previously identified: age, sex, type of tumor receiving RT, RT-early and late toxicity grade, any chemotherapy before surgery, ECOG, ASA score, Charlson comorbidity Index, creatinine, hydronephrosis, reason for cystectomy.

All tests were two-sided and a p value of < 0.05 was set to be statistically significant. All analyses were performed with SPSS 20 (SPSS Inc., IBM Corp., Armonk, NY)

1.2 Results

1.2.1 Study population and baseline characteristics

Twenty-five of 28 centers participated in this study. 682 valid cases were available. Six cases were excluded for missing of key data. Surgery was performed between the year 1984 and 2015. Surgery occurred after 2000 in 87.8% of patients. The median age of patients was 69.3 (IQR: 64; 77) and median age at RC differed significantly over the decades ($p < 0.001$; Table 1). Median follow-up time after radical cystectomy was 56 months (interquartile range: 22; 122). The mean follow-up time after radical cystectomy was 95±135 months.

Baseline demographic and disease characteristics are reported in Table 1. The majority of patients (49%) received RT for prostate cancer, while 27% of cases received RT for BC. Forty-four percent of the cohort had an ASA score >3 and 376 of

445 patients (84.5%) a Charlson Comorbidity Index >2. RT was administered to the pelvis in the majority of cases (87%), with only 4% of cases having RT to the abdomen with or without inclusion of the pelvis. Bladder cancer was the leading cause of cystectomy (63%), which was muscle invasive in 86% and NMIBC in 14%. BC developed after RT for other causes in 248 patients (36%). In total, 165 of 335 patients (49.3%) with previous prostate cancer, 31 of 67 patients (46.3%) with any gynecological tumor and 42 of 88 patients (47.7%) with any other cancer except BC, developed BC after RT for which cystectomy was indicated.

1.2.2 Complication and mortality rates

Table 2 presents an overview of all complications graded according to the Clavien–Dindo classification and time of complication onset. For 69 complications (6.1%), the time of onset was not available. In total, 682 patients experienced 1126 complications, mostly occurring in the first 30 days after surgery. The majority of complications were minor, but 29.6% experienced a Clavien >3 complication. A quarter of patients (24.6%) experienced more than one complication. The overall perioperative mortality rate was 2.9% in the first 30 days after surgery.

The medical complications, the associated Clavien grade, time of onset and reason for RT are reported in Table 3. At least one complication was observed in 52% of patients, which was grade III or higher in 11%. The most common complication was UTI/pyelonephritis, which occurred in 19% of cases, followed by renal failure (12%).

Postoperative bleeding was the most common surgical complication (14%), but Clavien >3 only in 1%. Bowel leakage (6.2%) and ureteral strictures (9.2%) were most frequent major complications. Bowel leakage occurred predominantly during the early postoperative period, while ureteric strictures were most frequently diagnosed after 30-days.

1.2.3 Urinary diversion

The frequency of different types of urinary diversion is reported in Table 1. Incontinent urinary diversion was established in over 86% of patients with ileal conduit diversion being most common (75%). Ninety-four patients (13.9%) underwent a continent urine diversion. Patients with incontinent diversion were older, had more early and late radiotherapy-induced toxicities, received perioperative chemotherapy less frequently, and were more likely to have preoperative hydronephrosis (all $p < 0.003$). There were also significant differences in ASA, ECOG and Charlson Comorbidity Scores (all $p<0.001$) between patients undergoing continent and incontinent diversion. The complication rate, however, was comparable between both types of diversions.

1.2.4 Predictors of complications

Table 3 summarize the medical and surgical complications stratified by the type of disease that was originally treated with RT. Overall, any complication after pRTC occurred more frequently in patients previously treated with RT for bladder cancer (81.4%) or gynecological tumors (82.3%) compared to prostate (70.8%), colorectal or other cancers (73.4%; $p=0.046$). There was no difference in the rate of major complications according to the site of radiotherapy. Stratification of complications by decade of surgery showed a significant increase in the major complication rate in the latest years ($p=0.027$). Mortality, overall complications and major complications ranged between 0–20%, 65–100% and 20–75%, respectively, across centers. On multivariable logistic regression analysis that adjusted for age, sex, reason for radiation and type of RT, only bladder cancer ($p=0.023$) served as an independent predictor for any complication after pRTC (Table 4). On multivariable logistic regression analysis that adjusted for the same factors, none of the parameters was an independent predictor for a major postoperative complication. RT dose and toxicity were not included in the models because too many values were missing.

2.Cystectomy in elderly

Despite all the advances in technology, RC remains a morbid procedure with complication rate and 30-day mortality raging from 30% to 60% and 1.1% to 5.2% respectively[26]. Age, comorbidities and tumor stage considerably affect the outcomes of RC. Nevertheless, a consistent portion of the literature supports the role of radical surgery in elderly patients[26]. Life expectancy is increasing rapidly in western countries and the number of BC diagnosis is going to be higher in the next years. Consequently, the urologists will be faced to a considerable number of people needing RC. In this framework, the clinician needs to accurately balance between risks and benefits of surgery in order to offer to the patient the best treatment option. There is still an open debate in the scientific community among the real impact of age in radical surgery for BC. Since chronological age does not reflect the biological one in an increasing number of people, age should not be considered as absolute contraindication to RC. In this framework, comorbidities and performance status play a crucial role in the decision-making process.

2.1 Materials and methods

This is a multi-center retrospective dataset including patients from 19 different centers. Patient ≥ 75 years old treated with RC for bladder cancer between 1990 and 2015 and with available information on comorbidities, pre surgical status and complications (according to Clavien scale) were entered in the database.

Individual patient data were requested for the following patient and tumor characteristics and were included in the database: age, sex, ASA score, ECOG score, Charlson comorbidity index, previous history of radiotherapy, neoadjuvant chemotherapy, pre-operative haematuria, pre-operative renal function, pre-operative haemoglobin (Hb), preoperative albumin, lymphadenectomy and its extension, intraoperative blood loss, transfusion rate, type of urinary diversion, results of pathology at cystectomy, postoperative renal function, postoperative Hb,

postoperative albumin. Multivariable regression analyses were carried out using the most important variables that had been previously identified: age, sex, previous RT, ASA score, ECOG, Charleston comorbidity index, previous lymphadenectomy, surgical approach, preoperative hydronephrosis, preoperative hemoglobin, preoperative creatinine, type of urinary diversion, clinical T stage, neoadjuvant chemotherapy.

Information on surgical complications was recorded according to the Clavien-Dindo classification[25] and classified according to the time of onset into early (within 30 days after surgery), intermediate (between 30 and 90 days) and late (more than 90 days).

The following end points were assessed: complication rate, overall mortality (OM) and cancer specific mortality (CSM).

Data quality control was carried out, and queries for inconsistent and missing data were sent back to the participating centers for resolution. All patients from centers with insufficient data quality were excluded.

2.2 Results

2.2.1 Baseline characteristics

Two thousand and six patients with a median follow-up 43months were entered in the database, 292 (14.6%) had≥85yrs. Baseline patients' characteristics are reported in table 5. Patients ≥85yrs had more preoperative hydronephrosis, hematuria and extravesical disease, and underwent more UCS diversion (22%). An open cystectomy was performed in 93% of cases and the specimen revealed an extravesical disease (≥pT3) in 18% of patients, 83% of patients received a contemporary lymphadenectomy. Mean intraoperative blood loss was 854.7cc (774.1).

2.2.2 Complications and mortality rates

Complication rates and time of onset are reported in table 6. Globally, 922 (46 %) experienced a complication and in the 39.7% of the cases occurred within the first month after surgery. Among patients with complication 381 (41.2%) had a Clavien≥3 and 36 (3.9%) had a Clavien V. 528 (57%) patients had more than 1 complication. Most common complications were urinary tract infection (9%), paralytic ileus (7.2%), low hemoglobin (6.9%), acute renal failure (5.4%) and enteric anastomosis leakage (4.3%). Categorization of complication according to Clavien, site and type are reported in table 7.

At multivariate analysis patients with ASA score <3 (OR 0.403, p<0.001), a localized disease (<pT3) (OR 0.278, p<0.001) and low comorbidity rate (Charlson<3) (OR 0.763, p<0.001) had a lower risk of both OM and CSM. Age did not affect both outcomes in multivariate.

Kaplan Meier curves are reported in figure 1 and 2.

3.Discussion

The results we presented derived from two high-volume series of radical cystectomy. Even if we did not include in the dataset a control group to evaluate differences in terms of complication and mortality, we can compare our data with the available literature.

We confirmed the general perception that pRCT is associated with a high risk of morbidity (75% risk of a single complication and a 33% risk of major complication)

and mortality (3.1% 90d mortality). The mortality rates almost overlap those of 2 reference series of radical cystectomies performed in a non-salvage setting [27, 28.]

On the other hand the complication rates reported in our savage series are higher compared to 50 and 64% reported in these two series, especially if we consider the major complication rates (nearly 3 times higher in our series compared with the 2 reference series) [27,28.]. Interestingly, these higher complication rates cannot be explained by higher baseline comorbidities in our cohort since the proportion of ASA score ≥ 3 and Charlson score ≥ 2 almost overlapped that of the reference series. Therefore, these data support the concept that pRTC is a more morbid procedure than non-pRTC.

We found that urinary diversion was the leading cause of surgical complications. The 6.2% rate of bowel leak appears significantly higher than the 1.7% documented in previous series [29], and if compared with non-salvage cystectomy groups. Similarly, in elderly patients the use of bowel in the reconstructive part of cystectomy was an independent predictor of complication at multivariate analysis. In our opinion, this predictable risk, leading to re-operation in a number of our cases, has to be clearly mentioned in the preoperative counseling of the patient.

In both of our series we reported complications according to the use Clavien system and this is a strength of our study. On the other hand, the retrospective data collection and the relatively long time span needed to collect a large series are an

unavoidable source of selection and information biases. Nonetheless, in order to have the highest quality reporting, we used the Martin's criteria and selected high-volume academic centers experienced with bladder cancer management, performing radical cystectomy procedure, and reporting post operative complications [30] . Another limit of our study is the lack of a control group to better evaluate the rate of complications and mortality.

4. Conslusions

The current understanding of factors impacting morbidity of radical cystectomy in fragile/complex patients is limited by the relative paucity of consistent series [31-34]. Different diseases may potentially account for different outcomes of RC as a result of variations in age of the patient, tumor biology and/or toxicity of different radiation therapy regimens.

Considering the group of patients with a previous history or RT, in half of the cases of our series cystectomy occurred after pelvic radiation prostate cancer. Interestingly, a previous radiation therapy for bladder cancer was associated with a higher risk of any complication after pRTC as compared to previous radiation for prostate cancer. In light of the potential growing indication for pRTC after RT for prostate cancer due to the widespread use of prostate radiotherapy, our data support the safety of this salvage procedure that was previously reported as highly morbid[35]. By the way, cystectomy after RT is globally associated with a high rate of major complication

that, contrary to some previous reports, dramatically exceeds that reported after cystectomy in patients without prior RT[36].

Considering both of our series, age should not be considered as an independent limiting factor to perform radical cystectomy. Moreover, the overall complication rates resulted quite lower than previously reported. According to our data, minimally invasive surgery still plays a marginal role in this group of patients. Robotic or laparoscopic cystectomy was performed only in few cases. Unfortunately, due to the lack of evidence in this field we cannot confirm that minimally invasive approach can reduce morbidity and mortality in fragile patients.

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Appendix 1.

Tables

Table 1

Baseline patient and disease characteristics of the entire cohort (N=682)

Variable	Categorization	N (when not otherwise indicated)	%
Age	Median (IQR)	69.3 (64; 77)	
	<50yrs. 51-75yrs. >75yrs.	38 (5,6) 435 (63,8) 209 (30,6)	
Sex	Male Female	565 117	82.8 17.2
Tumour type receiving radiotherapy	Bladder	187	27.4
	Prostate	335	49.1
	Colorectal	37	5.4
	All Gynaecological Uterus Cervix Vulvar	67 34 28 5	9.8 5.0 4.1 0.7
	Testicular	12	1.8
	Other	39	5.7
	Unknown	5	0.7
Radiotherapy type	EBRT	549	80.5

	Brachytherapy	55	8.1
	Brachy+EBRT	23	3.4
	Unknown	55	8.1
Radiotherapy dose (Gy)	Median; (IQR)	63 (51;70)	
	Missing value	409	60.0
Radiotherapy site	Prostate	214	31.4
	Pelvis	376	55.1
	Abdomen	20	2.9
	Abdomen & pelvis	6	0.9
	Perineum/vulva	5	0.7
	Other	1	0.1
	Unknown	60	8.8
Acute Radiotherapy GU toxicity grade	0 (none)	245	35.9
	1	54	7.9
	2	31	4.5
	3	26	3.8
	4	15	2.2
	Missing	311	45.6
Late Radiotherapy GU toxicity grade	0 (none)	221	32.4
	1	19	2.8
	2	71	10.4
	3	74	10.9
	4	13	1.9
	Missing	284	41.7
Chemotherapy (any before surgery)	No	452	66.3
	Yes	165	24.2
	Missing	65	9.5

Time from RT to cystectomy (months)	Median (IQR)	56.0 (21;121)	
Baseline ECOG	0	155	22.7
	1	136	19.9
	2	103	15.1
	3	8	1.2
	Missing	280	41.1
ASA score	1	42	6.2
	2	284	41.6
	3	286	41.9
	4	15	2.2
	Missing	55	8.1
Charlson score	Median (range)	3 (0-13)	
	Missing	237	34.8
Creatinine	Median (range)	1.0 (0.4-9.2)	
	Missing	300	44.0
Hydronephrosis	No	422	61.9
	Unilateral	130	19.1
	Bilateral	34	5.0
	Missing	96	14.1
Reasons for cystectomy	Bladder cancer	435	63.8
	Other malignancy	71	10.4
	Non cancer related	149	21.8
	Unknown	27	4.0
Pathology at cystectomy (bladder cancer only)	pT0	23	3.4
	pTa/pT1	90	13.2
	pT2	189	27.7
	pT3	49	7.2
	pT4	51	7.5

	Missing	21	
Type of urinary diversion	Ureterocutaneostomy	51	7.5
	Ileal conduit	519	76.1
	Ureterosigmoidostomy	1	0.1
	Neobladder	43	6.3
	Continent pouch	51	7.5
	Other	17	2.5
	Missing	0	
Continent vs incontinent urine diversion	Continent urinary diversion	94	13.9
	Incontinent urinary diversion	587	86.1

Table 2
Categorization of all complications in 682 radical cystectomy patients according to Clavien stratified by time of onset

Clavine grading of complications	**Total** N (%)	**≤ 30 d** N (%)*	**> 30/<90 d** N (%)*	**≥ 90 d** N (%)*
Total (Any Clavien)	1126 (100)	732 (100)	124 (100)	201 (100)
Clavien I	280 (24.9)	203 (27.7)	24 (19.4)	42 (20.9)
Clavien II	513 (45.6)	349 (47.7)	66 (53.2)	59 (29.4)
Clavien III	262 (23.3)	128 (17.5)	28 (22.6)	92 (45.8)
Clavien IV	38 (3.4)	30 (4.1)	1 (0.8)	6 (2.9)
Clavien V (death)	33 (2.9)	22 (3.0)	5 (4.0)	2 (0.9)
Clavien I or II	793 (70.4)	552 (75.4)	90 (72.6)	101 (50.2)
Clavien ≥ III	333 (29.6)	180 (24.6)	34 (27.4)	100 (49.8)

More than 1 complication (% of patients)	168 (24.6)	149 (21.8)	46 (6.7)	91 (13.3)

* Time of complication was not available for 69 complications.

Table 3
Medical complications stratified by type, Clavien grading, time of onset and type of disease for which RT was administered.

Medical complication	**Total** N (%)	**≤ 30 d** N (%)*; +	**30/90 d** N (%)*; +	**> 90 d** N (%)*;+	RT for prostate cancer **	RT for BC**	RT for gynaecol cancer**	RT for rectal and other cancer**
At least one complication (any Clavien)	359 (52.6)	283 (78.8) ++	35 (9.7) + +	83 (23.1) ++	157(49.4)	85 (58.6)	31 (50.0)	42 (53.2)
Pts. with more than one complication (any Clavien)	54 (7.9)	51 (14.2) ++	19 (5.3) + +	38 (10.6) ++	21 (6.6)	11 (7.6)	9 (14.5)	6 (7.6)
At least one complication Clavien ≥ III	121 (13)	51 (14.2) ++	7 (1.9) ++	25 (7.0) + +	34(10.7)	22(15.2)	5(8.1)	8(10.1)
Infection (total) any Clavien	171 (25)	96 (14.1)	19(2.8)	33 (4.8)	75(23.6)	40(27.7)	19(30.6)	18(22.9)
Clavien ≥ III	23 (3.4)	9(14.6)	4(49.2)	10(63.8)	20 (23.6)	17(11.8)	7 (11.3)	
Chest any Clavien	38 (5.5)	34 (91.9)	0	3 (8.1)	13(4.1)	9(6.2)	4(6.5)	3(3.8)
Clavien ≥ III	0	0	1 (33.3)	1 (33.9)	13(4.1)	9(6.2)	4(6.5)	3(3.8)

UTI/ pyelonephritis any Clavien	133 (19.5)	62 (48.1)	19 (14.7)	30 (23.3)	62(19.5)	31(21.5)	15(24.1)	15(19.1)
Clavien ≥ III	22 (3.3)	9 (14.6)	3(15.8)	9(29.9)	7(2.2)	8(5.6)	3(4.8)	1(1.3)
Renal failure any Clavien	83 (12.2)	53 (66.3)	6 (7.5)	20 (25)	23 (7.2)	34(23.5)	8(12.9)	7(8.9)
Clavien ≥ III	18 (2.6)	7(13.2)	2(33.3)	7(35.0)	9(2.8)	5(3.5)	2(3.2)	2(2.6)
Respiratory failure any Clavien	38 (4.2)	23 (3.4)	1 (0.1)	0	13(4)	5(3.5)	1(1.6)	2(2.6)
Clavien ≥ III	10 (1.4)	9(39.1)	0	0	5(1.5)	3(2.1)	1(1.6)	1(1.3)
Neurological any Clavien	77(4.6)	23 (79.3)	3(10.3)	3(10.3)	16 (5)	6(4.1)	2(3.2)	4(5.1)
Clavien ≥ III	6 (0.8)	5(21.7)	0	0	1(0.3)	2(1.4)	0	1(1.3)
Cardiac any Clavien	46(6.7)	39 (95.1)	2(4.9)	0	24(7.6)	7(4.9)	3(4.8)	6(7.6)
Clavien ≥ III	12(1.7)	10(25. 7)	0	0	8(2.6)	1(0.7)	1(1.6)	1(1.3)
Metabolic acidosis any Clavien	76(8.5)	46(82. 1)	3 (5.4)	6 (10.7)	14 (4.4)	36 (24.8)	2 (3.2)	3(3.8)
Clavien ≥ III	7(1)	5(10.8)	0	2(33.4)	4(1.2)	2(1.4)	1(1.6)	0
DVT any Clavien	26 (3.8)	13 (52)	4 (16)	8 (32)	9(2.8)	5(3.4)	2(3.2)	7(8.9)
Clavien ≥ III	2 (0.3)	2(15.4)	0	0	0	2(1.4)	0	0
PE any Clavien	10 (1.4)	8 (88.9)	0	1(11.1)	4(1.2)	2(1.4)	0	2(2.5)
Clavien ≥ III	3 (0.4)	2(25)	0	0	2(0.6)	1(0.7)	0	0

* Numbers not available for all cases.
+The same patient may had another complication at a different time (early, mid or late)
** Percent (%) numbers within each RT indication category. Missing information in 78 cases.

++ Percent (%) numbers among patients with at least one medical complication.

Table 4
Baseline patients characteristics according to the type of urinary diversion (incontinent versus continent)

Variable	**Incontinent N = 587**	**Continent N = 94**	**p**
Age Median (IQR)	72	62	<0.001
	66; 78	55; 69	
Sex Male Female	 491 (83.6) 96 (16.4)	 74 (77.9) 21 (22.1)	0.16
Tumour type receiving radiotherapy - Prostate cancer - Bladder cancer - Gynecological cancer - Other malignancies	 298 (51.2) 156 (26.8) 55 (9.5) 73 (12.5)	 37 (38.9) 31 (32.6) 12 (12.6) 15 (15.8)	0.173
Radiotherapy Early toxicity grade			<0.001
None	231 (39.4)	14 (14.7)	
1	54 (9.2)	0 (0)	
2	30 (5.1)	1 (1.1)	
3	26 (4.4)	0 (0)	
4	14 (2.4)	1 (1.1)	
Missing	90 (15.3)	33 (34.7)	
Radiotherapy Late toxicity grade			<0.001
None	207 (35.3)	14 (14.7)	
1	18 (3.1)	1 (1.1)	
2	69 (11.8)	2 (2.1)	
3	73 (12.4)	1 (1.1)	

4	11 (1.9)	2 (2.1)	
Missing	84 (14.3)	31 (32.6)	
Chemotherapy (any before surgery)			
Yes	143 (24.4)	52 (54.7)	0.001
No	400 (68.1)	22 (23.2)	
missing	44 (7.5)	21(22.1)	
Baseline ECOG			0.001
0	135 (23)	20 (21.1)	
1	121 (20.6)	15 (15.8)	
2	102 (17.4)	1 (1.1)	
3	8 (1.4)	0	
Missing	221 (37.6)	59 (62.1)	
ASA score			0.001
1	32 (5.5)	10 (10.5)	
2	250 (42.7)	34 (35.8)	
3	257 (43.9)	29 (30.5)	
4	14 (2.4)	1 (1.1)	
Missing	33 (5.6)	21 (22.1)	
Charlson score			
Median (range)	2 (0-13)	4 (0-8)	0.010
Missing	178 (30)	27 (29)	
Creatinine (mg/dl)			0.4 – 9.15
Median (range)	1.2 (0.42-9.1)	1.0	44.0
Missing	264 (45)	40 (42)	
Hydronephrosis			0.003
No	356 (60.9)	66 (65.9)	
Left	83 (14.2)	7 (7.4)	
Right	38 (6.5)	2 (2.1)	
Bilateral	34 (5.8)	0 (0)	
Missing	74 (12.6)	20 (21.1)	

Reason for cystectomy			0.367
Bladder cancer	372 (63.4)	63 (66.3)	
Other malignancy	59 (10.1)	12 (12.6)	
Non cancer related	130 (22.1)	19 (20)	
Unknown	26 (4.4)	1 (1.1)	

Table 5. Baseline patient's characteristics

Sex, male n (%)	1599 (79.7)
ASA score >2* , n (%)	985 (51.7)
ECOG , n (%) ECOG 0-2 ECOG 3-4	 1377 (97.5) 35 (2.5)
Charlson index*, mean (SD)	3.0 (2.9)
Neoadjuvant CT, n (%)	160 (5.3)
Previous RT*, n (%)	102 (5.3)
Preoperative hydronephrosis*, n (%)	553 (30.4)
Preoperative hematuria*, n (%)	477 (30.2)
ERAS protocol*, n (%)	168 (9.0)
Clinical T stage before surgery*, n (%) Localized to the bladder T3 or more	 1399 (82.0) 307 (18)
Preoperative creatinine*, mean (SD)	1.27 (0.59)
Preoperative hemoglobine*, mean (SD)	12.6 (2.2)
Preoperative eGFR*, mean (SD)	58.4 (21.3)
Preoperative albumine*, mean (SD)	4.0 (0.6)

Table 6. Classification of complications according to Clavien Dindo scale and time of onset.

Pat. with at least 1 complication, n (%)	922 (46.0)

Total number of complication, median (IQR)	2 (1; 3)
Patients with more than 1 complication, n (%)	528/922 (57.27)
Patient with at least 1 complication Clavien ≥3, n (%)	36 (1.79)
Time of complication, n (%) within 30 days more than 30 days complications occurred more than once	 796 (39.7) 312 (15.6) 526 (26.2)
Complication according to Clavien, n (%) I II III IV V	 156 (16.9) 386 (41.82) 233 (25.24) 112 (12.13) 36 (3.9)

Table 7. Categorization of complication according to Clavien, site and type. Here are reported the most common types of complication according to the site.

	Overall	Clavien I-II	Clavien III-IV	Clavien V
Cardiopolmunary, N (%) - Arrhytmia - Hypovolemic shock - Respiratory failure - Cardiac arrest	249 (12.5) 72 (28.13) 46 (17.49) 36 (14.06) 16 (6.25)	138 (55.4) 48 (34.78) 34 (26.64) 5 (3.62) 1 (0.72)	93 (37.3) 24 (25.81) 12 (12.90) 23 (24.73) 7 (7.35)	18 (7.2) 0 0 5 (27.78) 8 (44.44)
Lymphatic vascular , N (%) - Low hemoglobin - Post operative bleeding - Lymphocele - Deep vein thrombosis	275 (13.8) 133 (48.01) 32 (11.55) 29 (10.47) 22 (7.94)	244 (88.7) 131 (53.69) 23 (9.43) 16 (6.56) 22 (9.02)	30 (10.9) 2 (6.67) 8 (26.67) 12 (40) 0	1 (0.4) 1(100)
Neuroligic , N (%) -Altered mental status -Cerebrovascular accident -Mental confusion -Nerve injury	98 (4.9) 48 (48) 17 (17) 13 (13) 12 (12)	90 (91.8) 0 1 (50) 0 1 (50)	6 (6.1) 47 (52.22) 14 (15.56) 11 (12.22) 11 (12.22)	2 (2) 1 (50) 0 0 0

Muscoloskeletical, N (%) -Rabdomyolisis -Hiccups	3 (0.2) 1 (33.33) 1 (33.33)	3 (100) 1 (33.33) 1 (33.33)	0 0 0	0 0 0
Gastrointestinal , N (%) -Ileus (>4days) -Enteric fistula -Bowel obstruction -Nausea/vomiting	419 (21) 144 (33.49) 82 (19.07) 42 (9.77) 34 (7.91)	317 (75.7) 135 (42.45) 57 (17.92) 10 (3.14) 34 (10.69)	99 (23.6)	3 (0.7
Urologic, N (%) - Acute renal insufficiency - Hydronephrosys / obstruction - Ureteral stenosis - Ureteroenteric anastomosis leak	304 (15.3) 180 (.4.8) 62 (20) 40 (12.9) 27 (8.71)	148 (48.7) 78 (52.7) 30 (20.27) 1 (0.68) 8 (5.41)	153 (50.3) 27 (17.65) 30 (19.6) 38 (24.8) 19 (12.4)	3 (1) 3 (100)
Wound, N (%) - Dehiscence - Wound infection - Parastomal hernia - Incisional hernia	241 (12.2) 81 (34) 68 (27.7) 37 (15.1) 15 (6.12)	166 (68.9) 35 (22) 64 (38.5) 24 (14.4) 8 (4.82)	75 (31.3) 43 (57.3) 3 (4) 13 (17.3) 7 (9.3)	0
Infections/metabolic, N (%) - UTI - Sepsis - Pneumonia - Fever	401 (20.1) 179 (43.6) 71 (17.32) 44 (10.73) 36 (8.78)	343 (85.5) 170 (49.56) 28 (8.16) 43 (12.5) 35 (10.2)	49 (12.2) 4 (7.84) 36 (71) 0 0	9 (2.3) 0 7 (77.8) 1 (11.1) 0

Figure 1. Kaplan-Meyer curve on OM (months)

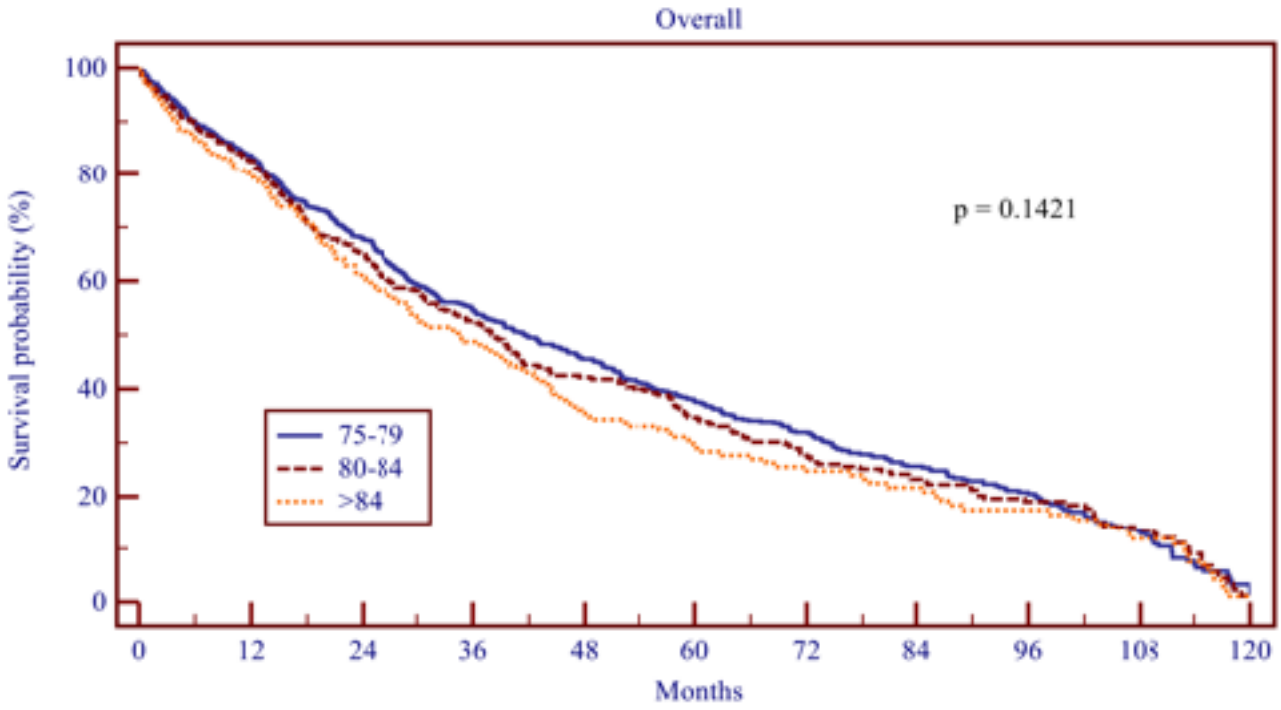

Figure 2. Kaplan-Meyer curve on CSM (months)