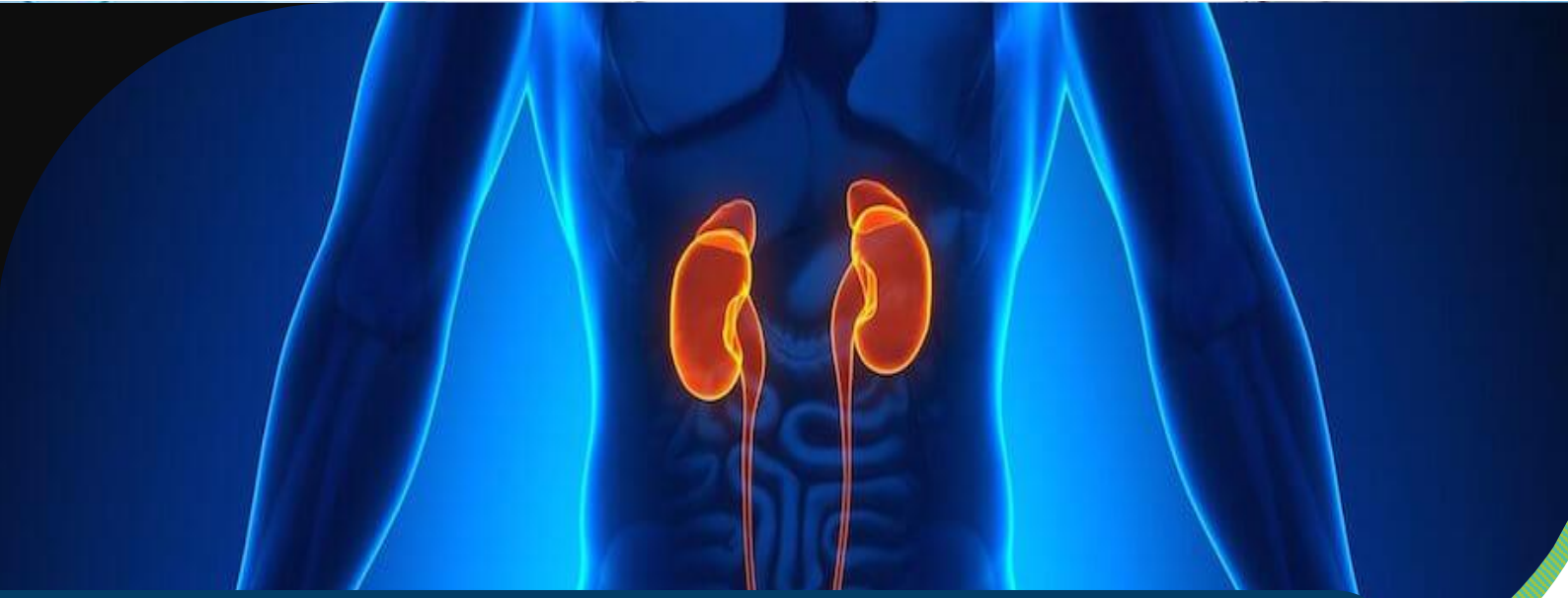

NU Rounds

Vol 1 | Issue 13 | 2020

Dear Doctor,

Greetings from Micro Labs limited. We are happy to bring you "**NU Rounds**" which contains latest and interesting news in the field of Urology.

Inside This Issue:

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Best Regards,

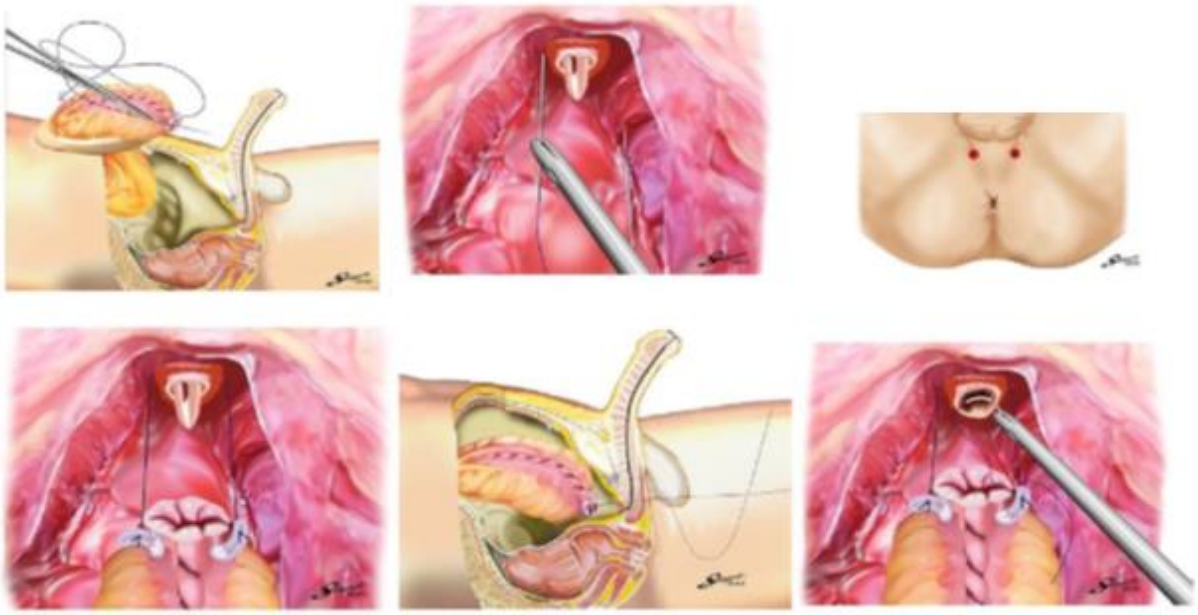
Medical Team, Micro Labs Ltd

New “double-pulling” method for neobladder-urethral anastomosis in laparoscopic

The rate of effective urinary diversion on the continent has recently been rising owing to developments in and standardization of the ICUD technique. While ICUD was promoted in RARC in a few high-volume centres, ECUD is more appropriate in RARC and LRC, as it has a lower complication rate at the moment. Nonetheless, intracorporeal NB-urethral anastomosis is physically problematic even in ECUD, since the pelvic room is restricted, so unnecessary stress between the NB and the urethra may occur. Recently a temporary single-pulling technique was released, which stabilized the NB and produced direct visualization of the anastomotic site without undue stress for intracorporeal NB urethral anastomosis. Here, they introduce a updated "transperitoneal double-pulling" procedure, which decreases the time needed for anastomosis of NB-urethral. They studied 23 instances of intracorporeal NB-urethral anastomosis conducted in LRC retrospectively with ECUD. The authors then studied single-pulling techniques (n = 8) and double-pulling techniques (n = 15), contrasting the time and problems of NB-urethral anastomose. In either case, they used a redesigned Studer NB, a spheroidal-shaped "heart-like" reservoir modeled by Bianchi et al. With the double-pulling technique, as mentioned below, they changed their previous single-pulling technique to promote NB-urethral anastomosis intracorporeally.

Two 70-cm 2-0 monofilament polypropylene sutures are positioned firmly at the 5 and 7 o'clock locations until the NB is inserted in the pelvic area, utilizing 6-cm straight needles which are not attached. Safe suture of approximately 2 cm long and maximum intestinal depth should be positioned so as not to break the NB neck wall. Hem-o-lok clips cover the bottom end and the needles are partially placed at the top of the NB (Fig.a) when the NB is positioned in the pelvic area and the peritoneum is expanded. At this stage, the two 6 cm straight needles are implanted behind the urethra's posterior wall (Fig. b), going through the perineal membrane, and then captured by an assistant with forceps (Fig. c). The NB is then taken nearer to the urethral stub by pushing the two softly

Suture loops, directing and stabilizing the NB neck (Fig. d, e). The NB collar is quickly defined and distinctly visualised as the cords are removed. The initial laparoscopic stitch for anastomosis is positioned between 4 and 6 o'clock in the urethra and the NB collar, while the assistant keeps the two supporting strings at the correct tension (Fig. f). The assistant retains this discomfort right over the posterior urethra anastomosis. Then the two sutures within the NB are cut and separated quickly.



(a) Two 70-cm 2-0 monofilament polypropylene sutures by 6-cm straight needle are applied to the wall of the NB neck at the 5 and 7 o'clock position.

(b) Two straight needles are placed temporarily behind the posterior wall of the urethra.

(c) A needle passed through perineal skin (red point) is caught by an assistant with forceps.

(d,e) The NB is brought down closer to the urethral stump by gently pulling out the two strings to guide and stabilize the NB neck.

(f) The initial laparoscopic stitch for anastomosis can be easily placed at the urethra and the NB neck at 4–6 o'clock.

The mean anastomotic period for double pulling (n = 15) was 22.5 min, slightly less than 43.5 min ($P < 0.01$) for single pulling (n = 8). This operation did not pose any perioperative risks. Postoperative anastomotic leakage happened in the single-pulling community in two situations (25 percent), and in the double-pulling category in one event (6.7 percent). Leakage of the three patients was cured after prolonged urethral catheter insertion; none required anastomotic re-stricture.

Laparoscopic intracorporeal NB-urethral anastomosis is difficult, and may be correlated with serious complications if undue stress is introduced between the NB and the urethra, if the NB does not sufficiently penetrate the urethra, or if strain-induced strictures form as a consequence of technological errors. With the single-pushing method, the NB has been pushed along the interior of the urethra by a rope to minimize the tension.4 The double-pulling technique enables the NB to be more firmly balanced and avoids movement by pushing two strings threaded via the perineal tissue. This makes for clearer representation of the NB face, even when there is unnecessary discomfort. Eventually, double-pulling anastomosis takes only twice as much time as in the single-pulling technique. There were numerous drawbacks to the present analysis.

There were only 23 patients in their case set, so their results of slightly reduced time for NB-urethral anastomosis in the above category might have impacted the learning curve. Given these drawbacks, their basic technique specifically encourages NB-urethral anastomosis in the laparoscopic intracorporeal. This innovative "double-pulling" technique helps to minimize suture and operational period and they agree that during RARC it has application in ECUD.

Source: Yanagisawa T, Miki J, Enei Y, et al. Novel "double-pulling" technique for neobladder-urethral anastomosis in laparoscopic radical cystectomy [published online ahead of print, 2020 Jul 11]. Int J Urol. 2020;10.1111/iju.14301.

Molecular characteristics and markers of advanced clear cell renal

INTRODUCTION

CCRCC is the most prevalent form of RCC, affecting 60–80 per cent of kidney cancers. RCCs are particularly immune to chemotherapy and radiation therapy, so early-stage disease care with surgical resection is routine. Cases of progressive and metastatic conditions, though, have restricted therapeutic choices, and long-term survival is about 10% for these cases. Sarcomatoid differentiation in RCC is known to be a high-grade tumor, grade 4 WHO / ISUP, with an aggressive nature even though the sarcomatoid differentiation portion is reduced in tumors, irrespective of the original tumor subtype. This comprises 15–20 per cent of RCCs in stage IV. This has weak prognosis, with a median lifespan of < 12 months, in line with its violent behaviour. While attempts to understand RCC 's molecular pathogenesis have demonstrated genomic heterogeneity in CCRCC, a subset of genes strongly linked to CCRCC's pathogenesis, including VHL, PBRM1, SETD2 and KDM5C, have been established. Recent studies have established potential genes which promote tumor growth and metastasis, including FOXO3a, and the CXCR2 and its ligand pathway. TP53 and PTEN were both involved with sarcomatoid differentiation in the pathogenesis of advanced CCRCC. The predictive and prognostic effects for metastasis of such genes have not been established however. Heterogeneity within and within CCRCCs reveals a branched evolutionary trend, indicating that CCRCCs lead to the parallel production and growth of specific tumor clones. The tumor microenvironment often tends to play a role in tumor heterogeneity, because specific genetic profiles have been found in the core tumor cells and peripheral cells. CCRCC demonstrates intratumoral and intertumoral variability of sarcomatoid distinction as well. A recent research indicated that sarcomatoid components contained in CCRCC have a specific mutational profile within the same tumor in approximately 41 per cent of cases as traditional CCRCC regions, indicating that both components have a shared origin cell. Nevertheless, within CCRCC sarcomatoid components have specific mutational profiles that are not present in the tumor 's traditional CCRCC regions. A new molecular study of CCRCC with sarcomatoid separation found that sarcomatoid derived CCRCC has a higher mutational burden relative to traditional CCRCC. Tumor heterogeneity in RCC faces significant obstacles for prognostic assessment and possible future goals for molecular therapy. It is difficult to evaluate the influence of the breadth of genomic heterogeneity (especially in advanced CCRCC with sarcomatoid differentiation) on the efficacy of targeted therapies, resistance and prognosis of candidate tyrosine kinase.

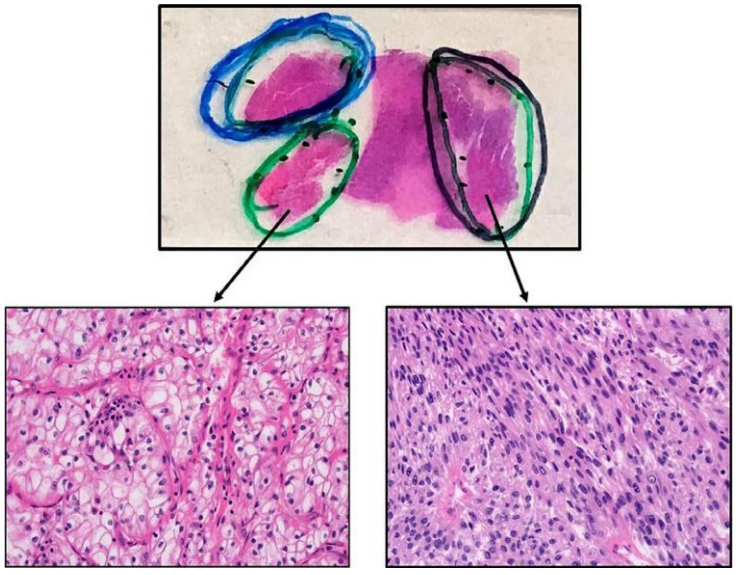
In this thesis the authors based their mutational research on a subset of genes highly important to CCRCC pathogenesis. Using the Illumina HiSeq tool and the Galaxy workflow, they analyzed 217 large tumor parts of traditional CCRCC (n=20) and a subset of other forms of RCC (n=5) from FFPE tissues, and established a possible metastasis marker in CCRC.

METHODS

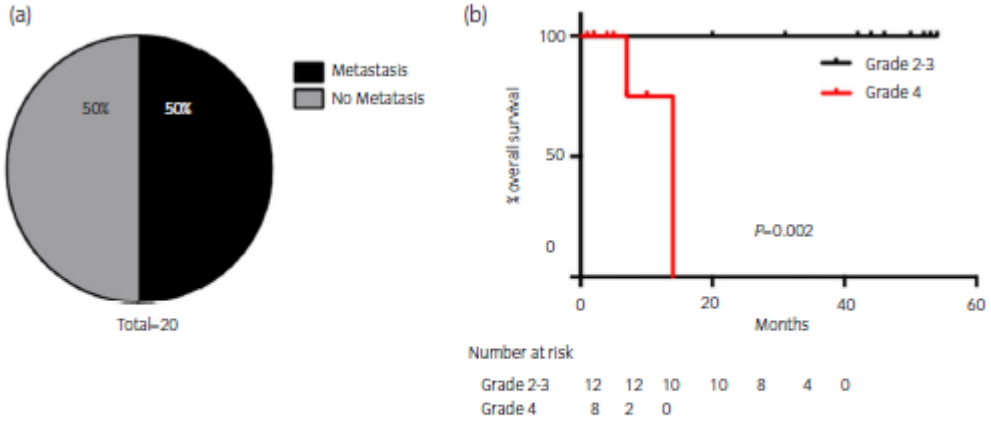
They carried out genomic analysis of 217 tumor foci from 25 patients with conventional clear cell renal cell carcinoma (14 patients), clear cell renal cell carcinoma with sarcomatoid differentiation (six patients) and non-clear cell renal cell carcinoma (five patients). Each tumor nodule on the tissue block that corresponded to the same focus on the slide was separated from the normal parenchyma and other histologically distinct areas of tumor. The isolated tumor foci were used for subsequent analyses and sequencing. Deoxyribonucleic acid from the formalin-fixed paraffin-embedded tissues was extracted. Multiplex bar-coded polymerase chain reaction amplification was carried out using next-generation sequencing libraries.

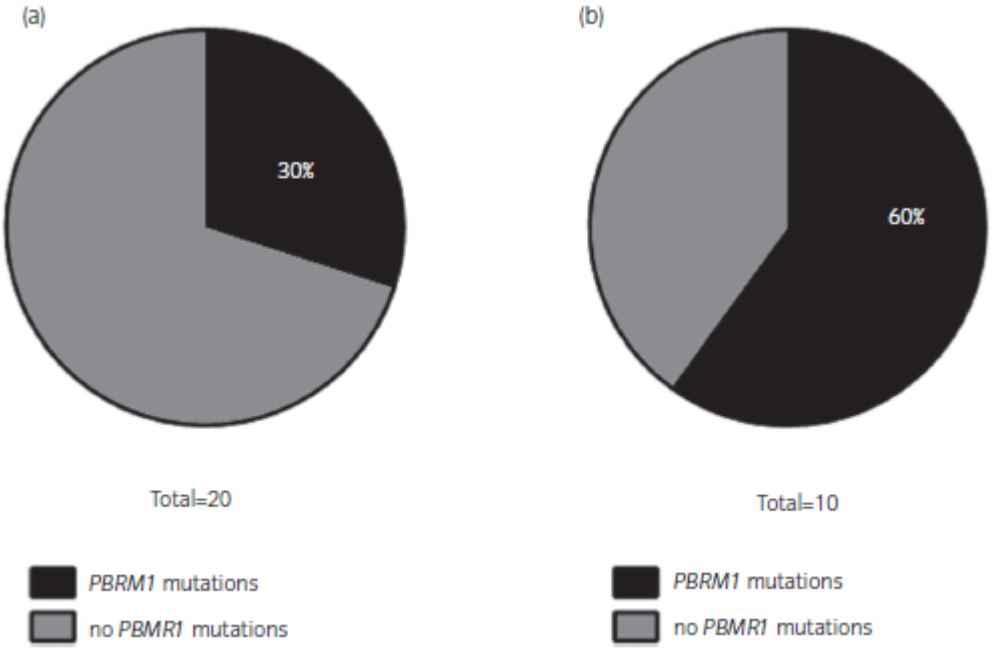
RESULTS

Overall, 67 protein alterations, including amino acid alterations, frame shifts and splice site mutations in seven genes were identified in the cohort of renal cell carcinoma tumors included in this study. Fewer patients with clear cell renal cell carcinoma with sarcomatoid differentiation had clear cell renal cell carcinoma-related mutations in comparison with patients with conventional clear cell renal cell carcinoma. Additionally, the average number of unique clear cell renal cell carcinoma-related protein alterations per patient was significantly lower in clear cell renal cell carcinoma with sarcomatoid differentiation than in conventional clear cell renal cell carcinoma. Mutations in PBRM1 were identified in a higher proportion of patients with high-grade tumors (World Health Organization/International Society of Urological Pathology grade 4) and in the primary tumors of six of 10 (60%) patients with metastatic disease.



Histological and morphological features of tumor foci in CCRCC. Representative histological features of different tumor foci from which genomic sequencing was carried out in one of the several cases.





Clinical outcome of localized and advanced CCRCC. (a) Proportion of CCRCC with metastatic disease. (b) Kaplan–Meier curve of overall survival of low-grade (WHO/ISUP grades 2– 3) and high-grade (WHO/ISUP grade 4) CCRCC.

CONCLUSIONS

Although there are drawbacks induced by intratumoral variability and selection prejudice, PBRM1 mutations may be correlated with metastasis and violent Simple Renal Cell Carcinoma cancer.

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Obeng RC, et al. Molecular characteristics and markers of advanced clear cell renal cell carcinoma: Pitfalls due to intratumoral heterogeneity and identification of genetic alterations associated with metastasis. Int Jour Urol. 2020 [Published online Jul 2020]. DOI: 10.1111/iju.14302.

PD-L1 expression and pattern of immune cells in pre-treatment specimens are associated with disease-free survival for HR-NMIBC undergoing BCG treatment

INTRODUCTION

Immune system plays a role in the diagnosis of non-muscle invasive bladder cancer (NMIBC), and this has been used with intravesic Bacillus Calmette – Guerin (BCG) instillations (IBI) for more than 40 years. Such non-specific immunotherapy, designed to attract immune cells (IC) into the bladder, is not ideal and in high-risk NMIBC (HR-NMIBC) the failure rates are similar to 50 per cent. Such deficiencies are possibly clarified by the escape of cancer cells from the patient's immune system, attributable in particular to couples of receptor-ligating CTLA4 / B27 and PD-1 / PD-L1. Such receptor-ligating couples may be inhibited by immuno-oncotherapy, which came for the most advanced stages of urothelial carcinoma in 2010–2015. The enthusiasm around the clinical development of this therapy has led to it now being investigated in the early stages of bladder cancer.

PD-L1 is a membrane protein expressed by cancer cells. Like other membrane proteins, it is possible to determine its level of expression using immunohistochemical techniques: an antibody directed against PD-L1 associated with a dye binds to the protein and quantification of staining on the slide by a pathologist makes it possible to define a score. Depending on the immuno-oncotherapy delivered to the patient, the score takes into account PD-L1 expression, in the tumour cells (TC) or in the tumour microenvironment (TME). Not surprisingly, the level of labelled cells varies from one patient to another. Therefore, the approximate incidence of PD-L1 + patients (i.e. those who may be regarded as potential candidates for immuno-oncotherapy) varies from 25 per cent when the procedure correlated with atezolizumab is tested to 55 per cent with durvalumab care scores in metastatic bladder cancer. If PD-L1 / PD-1 blockade response levels are from 15–20 percent, predictive activity biomarkers, like PD-L1 speech, remain uncertain. PD-L1 + patients should not be treated universally in the context of clinical treatment, but should be regarded according to the form of immuno-oncotherapy they would choose to recommend. Here they assessed the association using validated methods between both expression of cancer cell and TME and disease-free survival (DFS) in HR-NMIBC patients treated with IBI.

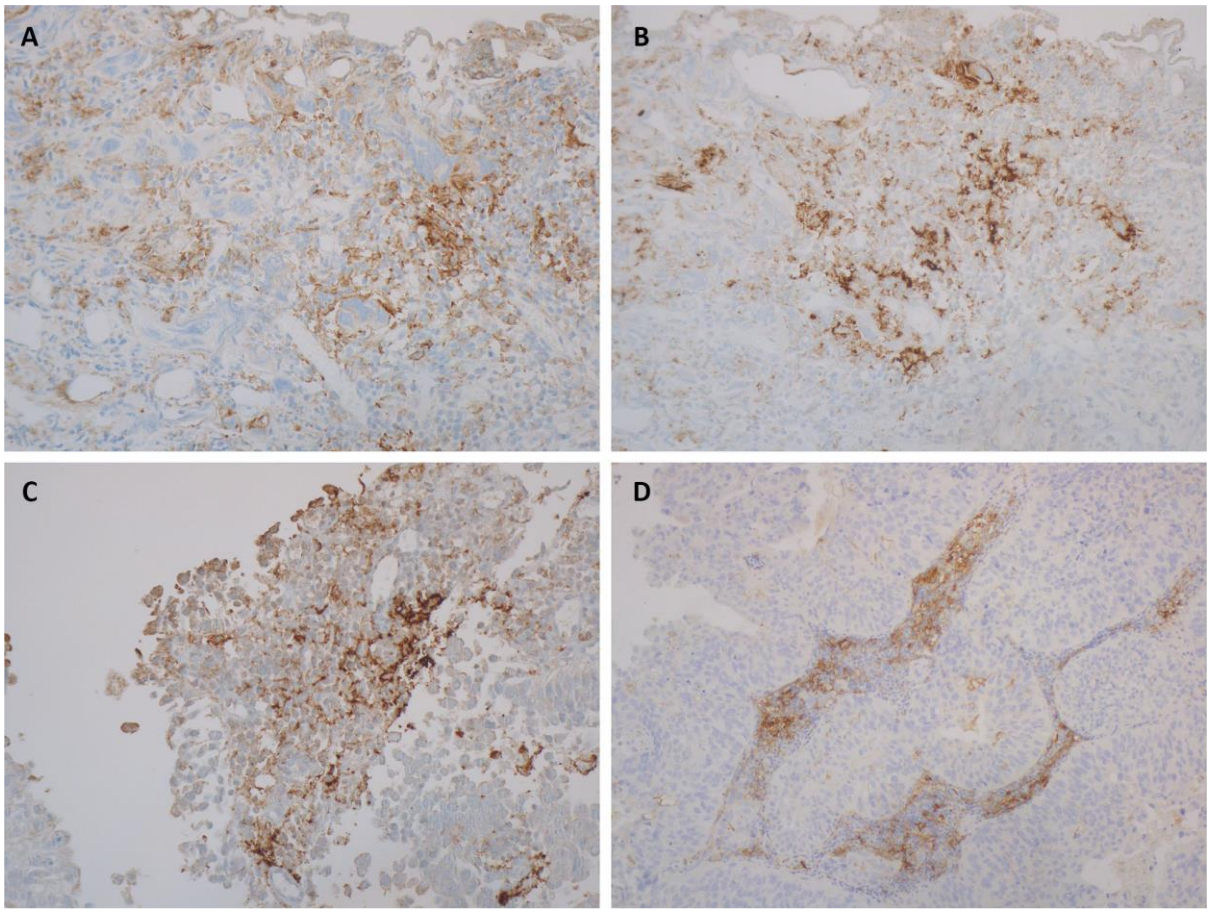
METHODS

Retrospective study in five French centres between 2001 and 2015. Participants were 140 patients with histologically confirmed HR-NMIBC. All patients received induction and maintenance IBI. Pathological stage/grade, concomitant carcinoma in situ, lesion number and tumour size were recorded. CD3, CD8 and PD-L1 expression in tumour cells and in T cells in the tumour microenvironment (TME) was determined immunohistochemically.

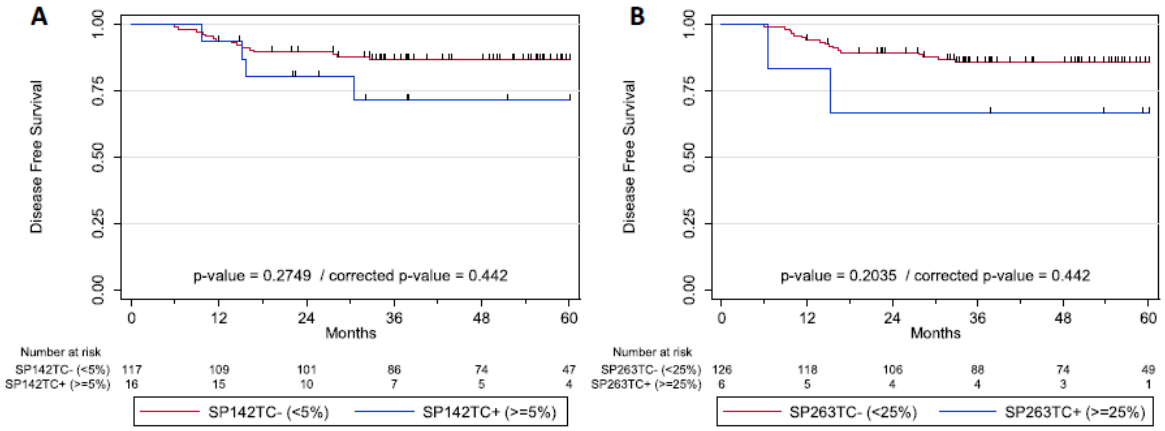
Median follow-up was 54.2 months. The primary outcome measure was DFS. Univariable and multivariable analyses were performed using the log rank test and Cox proportional hazards model.

RESULTS

Of the 140 NMIBC, 52 (37.1%) were Ta, 88 (62.9%) were T1 and 100% were high grade. Median number of maintenance IBI was six (range 1–30). Twenty-five (17.9%) patients had recurrence/progression. In multivariable analysis, age (HR 1.07 [95% CI 1.02–1.13], p = 0.009), PD-L1 expression in tumour cells (HR per 10 units = 1.96 [95% CI 1.28–3.00], p = 0.02) and CD3/CD8 ratio (HR per 10 units = 3.38 [95% CI 1.61–7.11], p = 0.01) were significantly associated with DFS. However, using the cut-off corresponding for each PD-L1 antibodies, PD-L1 + status was not associated with DFS.



Immunohistochemistry: membranous staining of tumor cells, not all tumor cells display staining with different antibodies: 28 8 (a), SP263 (b), E1N3L (c). Expression of SP142 is negative in the tumour cells but postive in the lymphocytes surrounding the tumoral tissue



Kaplan–Meier disease-free survival curve according to PD-L1 + status in tumour cells. a SP142 antibody PD-L1 + IC ≥ 5%, b SP263 antibody PD-L1 + TC/IC ≥ 25%

CONCLUSION

With a correlation in HR- NMIBC between PD-L1 expression and BCG loss, the PD-L1 + status was not a prognostic factor in BCG response. In addition, they verified the important function the IC plays in the treatment of BCG inside the microenvironment. Such results demonstrated the reason for coupling anticorps BCG and PD-L1 / PD-1 in early cancer of the bladder.

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Roumiguié M, et al. PD-L1 expression and pattern of immune cells in pre-treatment specimens are associated with disease-free survival for HR-NMIBC undergoing BCG treatment. World J Urol. 2020. https://doi.org/10.1007/s00345-020-03329-2