

## CHECK CYSTOSCOPY FOLLOW-UP PRACTICE FOR LOW-RISK (pTa) NON-MUSCLE INVASIVE BLADDER CANCER IN THE UNITED KINGDOM: THE NICE OR THE EUROPEAN GUIDELINES?

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### Abstract

**Objectives:** To identify the best practice policy and guideline for surveillance with check cystoscopies follow up for low-risk pTa urothelial bladder tumour and to identify the recurrence rate and the progression rate of low-risk urothelial bladder tumour and how safe is it to discharge them at 1- versus 5-years of follow up.

**Primary outcome:** The primary goal is to assess both the rate of recurrence and rate of progression of low-risk Non-Muscle Invasive Bladder Carcinoma (NMIBC) during the first 5-year after initial Trans-Urethral Resection of Bladder Tumour (TURBT) and how safe is to discharge this class of group after one year versus five years of surveillance and compare it to previous reports.

**Secondary outcome:** To estimate the cost-effectiveness of a reduced follow-up scheme, if this is deemed a safe practice to follow.

**Methodology:** It is a single centre, retrospective review of all low-risk NMIBC patients diagnosed with low-risk bladder tumors at our Trust between 2012 and 2014 from our local urological cancer multi-disciplinary team (MDT) registry and ensured a 5-year time-lapse from diagnosis. Histology grade and staging from the first TURBT, receiving of mitomycin within 24 hrs following the initial TURBT, the timing of cystoscopy follow-up, cystoscopy findings (evidence of recurrence), further procedures (bladder biopsy, fulguration or TURBT), histology of further procedures, recurrence rate and time from the first TURBT to discharge to primary care are reviewed and analysed.

**Result:** Our initial review revealed a high likelihood of recurrence (33.9%) in the low-risk NMIBC patients after 12 months of being cancer free. It also demonstrated that there is further progression in (23.8%) of those who had a later recurrence despite being asymptomatic.

**Conclusion:** We would recommend a 5-year follow-up surveillance and further national collaboration to audit this patient subgroup to define a safe period of cystoscopic follow-up for these patients and bring further evidence for NICE to build up their recommendations.

**Keywords:** *Low risk, Bladder tumour, Cystoscopy follow-up, Recurrence, Tumour progression*

## INTRODUCTION

International Agency for Research on Cancer (IARC) reports that bladder cancer is the 10th most diagnosed cancer worldwide and the 7th most frequently diagnosed cancer in men worldwide. In the United Kingdom, according to data from Cancer Research UK in 2018, there are approximately 10,300 new cases of bladder cancer diagnosed annually, and it was ranked as the 11th most common only diagnosed cancer, with almost about 28 cases every day.<sup>1</sup>

NMIBC is a type of cancer that develops in the tissues lining the mucosa of the bladder, and muscles are spared from this cancer. Still, overall incidences are lower when both genders are considered, and in this case, it ranks as the 10th most diagnosed cancer globally. According to European Association of Urology (EAU), the incidence rate of bladder cancer (age-standardized) is 9.5 in males and approximately 2.5 in females. The rate in European Union is higher, with 20 for males and 4.5 for females.<sup>3</sup> The mortality rate for bladder cancer was reported to be 3.3 for males and 0.86 for females. This represents that women are way less affected by this type of cancer than men; thus, men have higher mortality rates than women. The rate of incidence and mortality rate is not consistent throughout the world. Still, it varies, and many factors such as risk factors, timely detection, diagnostic measures and treatment facilities are available. It also depends on the access of people to healthcare and diagnostic facilities. According to reports, approximately 75% of patients suffering from NMIBC have a condition confined to the mucosal layer of the bladder (stage Ta or carcinoma in situ [CIS]) or submucosal layer called lamina propria (stage T1). In patient groups younger than 40 years, the percentage appears to be even higher than this. Mortality is usually correlated with the staging of the tumour. Patients with a Ta, T1 and CIS tumour are less likely to have cancer-related mortality, and survival rates are comparatively higher along with the prevalence.<sup>3</sup>

This study aims to compare the current guidelines for checking cystoscopy follow-up after the tumour resection with and without adjuvant chemotherapy for predictive purposes and as a tool to check for the recurrence and progression of the low-risk group of this disease. In some cases, there are many other

techniques for this purpose, such as cytology, urinary markers, and imaging scans. However, cystoscopy remains the gold standard for urological surgeons and oncologists for this purpose. In addition, ultrasound scans, computed tomography, and magnetic resonance imaging are also employed sometimes. Still, it has many limitations, and thus experts rely on check cystoscopy for follow-up purposes to see if the patient has developed another tumour following the resection and/or chemotherapy.<sup>4</sup>

In a nutshell, the supporting evidence for how long the follow-up should last for the patients after initial treatment using cystoscopy and cytology is not robust. The frequency and duration of the procedures are very high in studies reporting any solid evidence, and this brings the discussion down to patient discomfort and the cost of getting these follow-up procedures for a long time.

## METHODOLOGY

It is a single-centre, retrospective review of all low-risk, NMIBC-diagnosed with low-risk bladder tumors at a busy teaching hospital in the North West of England between 2012 and 2014 from our local urological cancer MDT registry. Our Trust had its own local guidance to follow up with this group of patients for 5 years; hence it was ensured that there was a 5-year time-lapse from diagnosis. All patients with G2 (high grade) or G3 will fall into the intermediate and high-risk groups and hence be excluded. In addition, the exclusion criteria involved any solitary (>3cm) or multifocal tumour on the first diagnosis and any concomitant CIS plus any recurrence within the first year as well (as they will be upgraded to intermediate risk). The clinical notes, level of surgeons performing the procedure, either consultants or middle grade or specialty trainee level under supervision or not have also been considered, histology grade and staging from the first TURBT, receiving of mitomycin C (MMC) within 24hrs following the initial TURBT, timing of cystoscopy follow-up, cystoscopy findings (evidence of recurrence), any interim symptoms, further procedures (bladder biopsy, fulguration or TURBT), histology of additional procedures, recurrence rate and time from the first TURBT to discharge to primary care.

All the above were reviewed and analysed to answer the research question and help us reach a recommendation and a conclusion.

### RESULTS

In this study, a total of ninety-eight patients diagnosed with low-risk NMIBC from 2012 to 2014 were identified, of which 76 (77.5%) were male, and 22 (22.5%) were females. The average age was 70 years (40-91), and the median age was 72 years. All patients had cystoscopic follow-ups for 5 years per our local hospital protocol.

Of the initial group, we had 21 patients with bladder cancer recurrence within the first 12 months, leaving a cohort of 77 patients for review. However, a further 15 patients were excluded as they missed their follow-up between the 2nd and 5th year (nine patients died before completing the follow-up for a reason other than bladder-cancer-related death, and 6 patients had moved from the local hospital area to a different region) leaving a final cohort of 62 patients to sub-analyse, all of which completed a cystoscopic check examination for the full five years as per our local hospital policy.

Reviewing the notes of these patients retrospectively, it was highlighted that 21 patients (33.9%) had their recurrence after the first 12 months of being cancer free. It was also observed that 5 of these 21 patients (23.8%) have progressed to a higher-grade tumour after being tumour free for the

first 12 months from primary diagnosis. Mitomycin C instillation drug has been given to 15 patients within the first 24 hours of primary trans-urethral resection of bladder tumour (TURBT). The rest of the 6 patients have not received MMC either due to deep resections or signs of haematuria directly following the procedure. No Photo Dynamic or Narrow Band Imaging scopes were used during the initial treatment or follow up for our patients.

Of the 21 patients with recurrences beyond the first year, it is found that 16 patients have remained at the same grade and stage, while 5 patients have shown progression of the disease to a higher grade, in which two cases have progressed from low-grade G2pTa to multifocal G3pT1, other two have progressed from low-grade G2pTa to G3pTa, and one progressed to multifocal high-grade G3pTa+CIS from low-grade G2pTa (i.e., all progressed to high grade and risk of NMIBC). Interestingly all the five cases with progression had received MMC no later than 24 hours after their initial surgery. The median average recurrence was between 1.3 and 5.9 years (3 years). The follow-up average for the patients with check cystoscopies ranged between 59 to 71 months.

### CORRELATION

The correlation coefficient value for Pearson's test revealed the recurrence and mitomycin C instillation and tumour size as weak negative relation (Tables 1 and 2). The tables indicate that there is

**TABLE 1** Age, recurrence and tumour

Correlations				
		Age of respondent	Recurrence	Tumour size
<b>Age of respondent</b>	Pearson Correlation	1	.231*	.053
	Sig. (2-tailed)		.022	.607
	N	98	98	98
<b>Recurrence</b>	Pearson Correlation	.231*	1	-.021
	Sig. (2-tailed)	.022		.834
	N	98	98	98
<b>Tumor size</b>	Pearson Correlation	.053	-.021	1
	Sig. (2-tailed)	.607	.834	
	N	98	98	98

\*Correlation is significant at the 0.05 level (2-tailed)

**TABLE 2** MMC, staging and recurrence

Correlations				
		Tumour size	Mitomycin C instillation MMC	Recurrence
Tumor size	Pearson Correlation	1	-.157	-.021
	Sig. (2-tailed)		.123	.834
	N	98	98	98
Mitomycin C instillation MMC	Pearson Correlation	-.157	1	-.182
	Sig. (2-tailed)	.123		.073
	N	98	98	98
Recurrence	Pearson Correlation	-.021	-.182	1
	Sig. (2-tailed)	.834	.073	
	N	98	98	98

no null value. The correlation values turn out weak negative whereas, the significance is tested through sig. (2-tailed). The standard alpha value is 0.05, and on the other hand, it shows the correlation value between recurrence and mitomycin C instillation as  $-.157$  and  $-.021$ , which shows the weak negative relationship between these variables indicates no true significance. All these available for Pearson correlation indicates that weak negative relation between tumour size, mitomycin C instillation, and recurrence.

#### *Age and date of diagnosis*

Figure 1 shows the respondent's age and the year of tumor diagnosis among the respondents. It indicates that most diagnosed patients are around the age of 70, and the maximum age of the respondent is 90 when they diagnose with the tumor.

Figure 2 shows the date of the diagnosis, the recurrence level among the respondents, and the date of tumor diagnosis. This indicates that most of the patients had a tumor recurrence in 2014.

Figure 3 shows the age and recurrence level among the individuals. It indicates that people over 70 have a higher recurrence ratio.

## DISCUSSION

Low-risk urothelial bladder tumours are those with low-grade differentiation, less than 30 mm in size, and do not invade lamina propria. Due to high chances of recurrences in patients diagnosed

with low-risk NMIBC, there is a general consensus by both EAU and NICE for regular follow-up. Both recommend regular check cystoscopic examination under local or general anaesthesia to keep a check on the intravesical recurrence of the tumour. However, the frequency and intensity of follow-up are different per the guidelines of EAU and NICE. Both have different follow-up regimes for the patient post-treatment. The level of risk in such patients is determined through risk tables, and follow-up frequency is decided based on that. People with low-risk tumours often have a lower number of follow ups and high-risk individuals are monitored closely to reduce the morbidity and mortality that could be associated with delayed diagnosis of disease recurrence.

In the low-risk group: both EAU and NICE advise check cystoscopy at three months, followed by the subsequent follow-up after 12 months post tumour resection (TURBT). If the follow-up at 12 months does not demonstrate any recurrence, NICE advises to discharge these patients back to primary care with no further cystoscopic examination. The practice is based on research suggesting that in cases where the tumour recurs after one year in patients within low-risk groups, it is usually the same low-risk stage and grade, and the patient will have the characteristic recurrent symptoms, such as haematuria. However, this is not the case in our centre where recurrence and progression were observed beyond 12 months despite being asymptomatic, but there

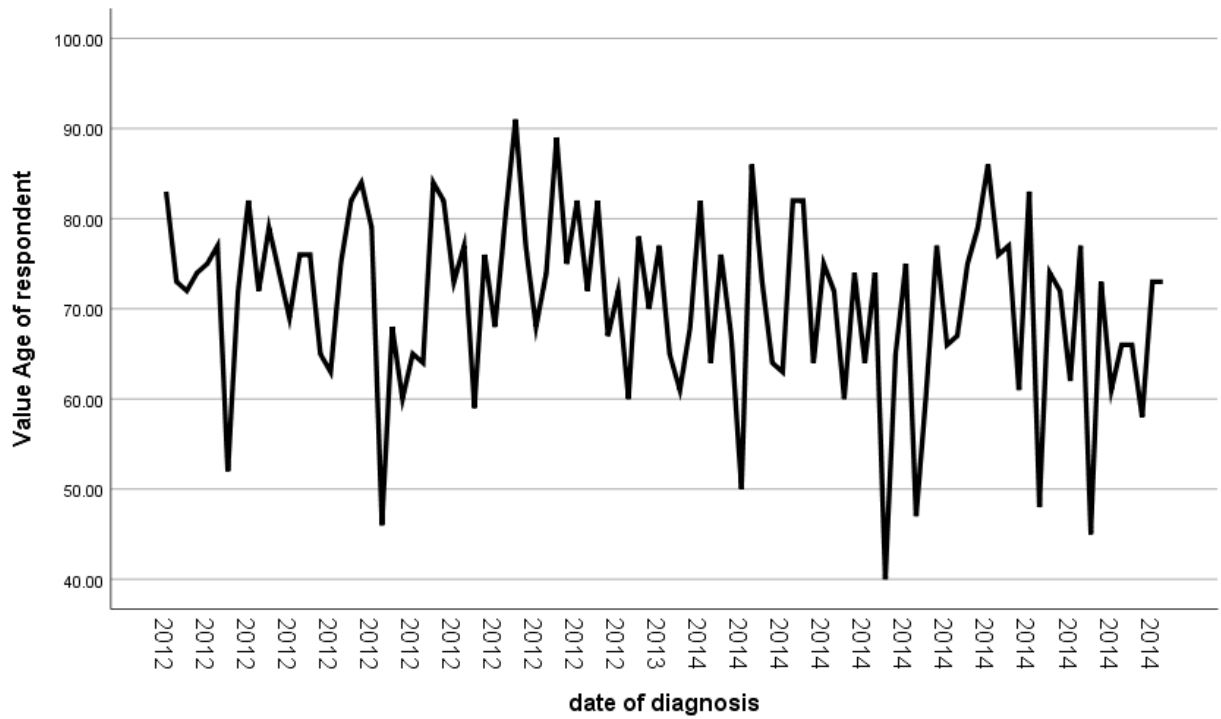


FIGURE 1 Age and date of diagnosis.

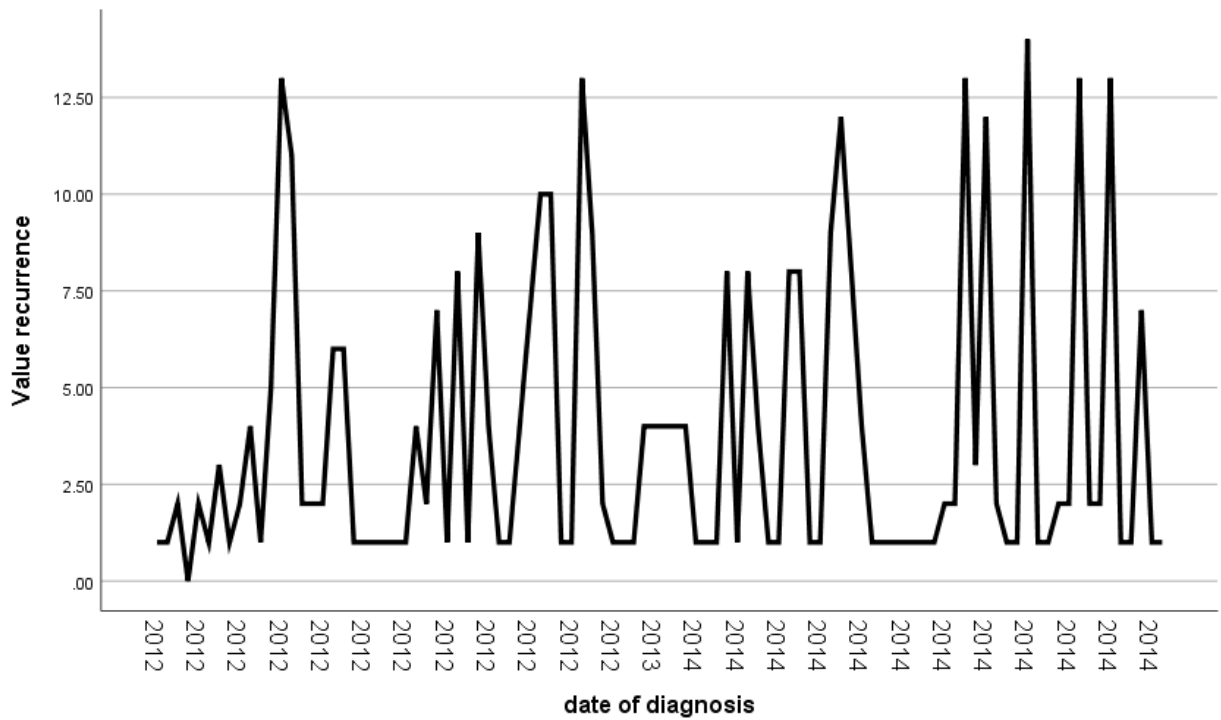
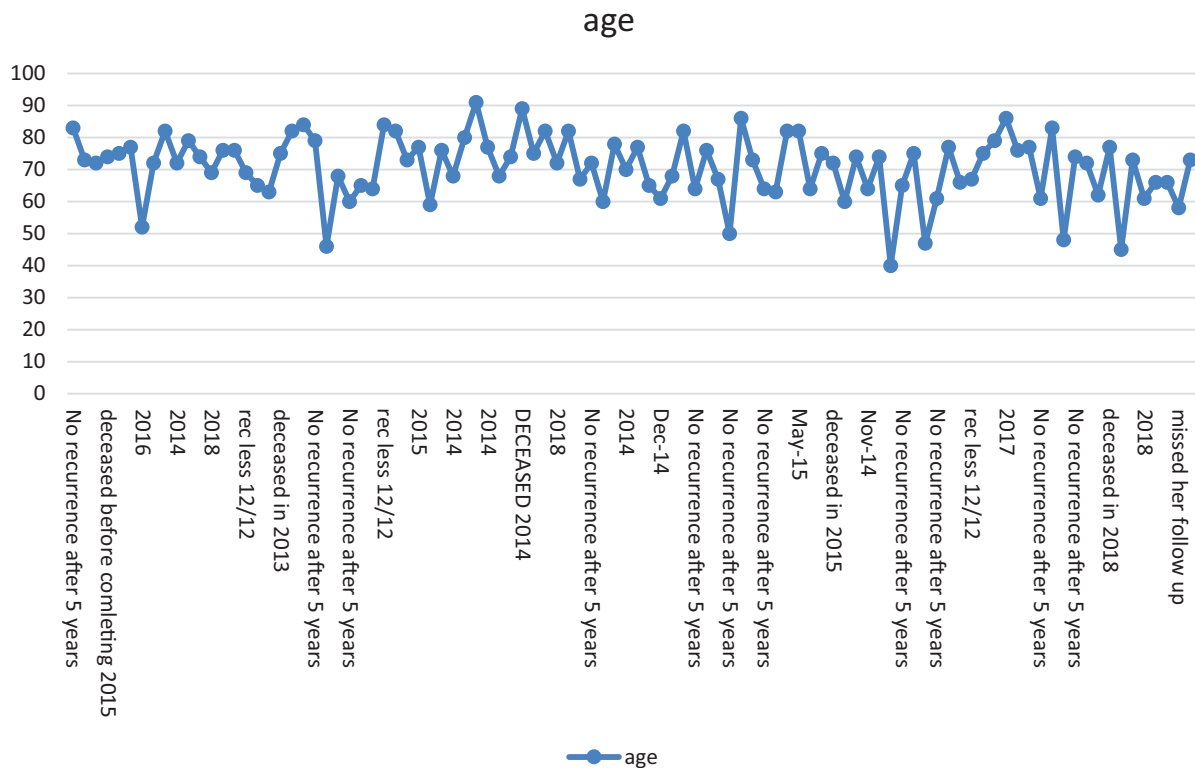


FIGURE 2 Recurrence and date of diagnosis.



**FIGURE 3** Age and recurrence.

is evidence that people who have been recurrence-free for five years have a very low risk of later recurrence; thus EAU believes that discharging the patient after 5-year surveillance can be considered relatively safer. That’s why EAU recommends regular annual checkups for five years to monitor for any recurrence.<sup>2</sup>

The practice varies across the country, and each hospital and region has its own preference. There is increasing observation and awareness of the different recommendations between NICE guidelines, which are based on the evidence that after one year, recurrence in low-risk patients is low grade and non-life threatening so that patient can be discharged<sup>5,6</sup> versus the EAU guidelines that recommend continuing further follow up annually for up to five years before discharging to primary care, that is based on evidence that recurrence is very low after 5 years.<sup>7</sup>

Oosterlinck W et al. have found that a low-grade tumour can transform into a higher grade and stage tumour, although it has been observed in less than

20% of cases over the years. The research also states that the chance of recurrence is higher within the initial two years and begins to reduce in the third year and a few after that.<sup>8</sup>

The advantage is to reduce the number of delayed diagnoses for low-risk bladder tumour recurrence for people who have already been discharged from further follow-up. It was observed in a few local trust hospitals that the number of recurrences is not low. Still, no clear study or data has been conducted to confirm whether this number warranted us to amend the national guideline.<sup>9</sup> Missing diagnosis for discontinued follow-up with tumour progression to the same or advanced stage would also significantly impact both patients’ health and the NHS system.<sup>10</sup>

Mariappan et al. studied a group of 115 patients for 25 years. They found that significant recurrence rates occurred in the first three months, and the absence of tumour recurrence at one year was also a good prognostic value. Out of 66 patients with five years follow-up, eight were found to have recurrence

between 1-5 years. In addition, the authors found that patients who were free of tumours for 5 years were tumour-free for 20 years. However, there were many limitations to the study, such as a small sample size and a loss of follow-up of about 40% with no intention to treat analysis.<sup>11</sup>

In contrast, a study conducted in Canada involved 152 patients with low-grade Ta, 45 patients were reported to have a recurrence after completion of successful 12 months, where eleven patients (13%) had recurrence between 12 and 24 months, 22(27%) patients had recurrence between 24 and 60 months. Interestingly, 12 patients (14%) developed cancer even after five years of follow up, wherein the tumour had progressed. The authors recommended continuing further follow-up.<sup>12</sup>

Another study was conducted to understand the relationship between age and bladder cancer behaviour in patients. The study tried to understand if tumour recurrence and progression are different in patients of different ages. The study's main objective was to see how the tumour behaves in different age groups and draw a comparison between different age groups. The study was conducted on 239 patients treated at the facility between 1994 and 2014. Based on their age, patients were organised into three groups. Group 1 had patients with ages  $\leq 40$  years, Group 2 had patients between 41 and 59 years of age, and Group 3 had patients with ages  $\geq 60$ . The study featured 207 patients with NMIBC, the most common (86.6%). It was observed that tumour recurrence time was different in all three groups ( $p = 0.001$ ). But it was noted that there was no significant difference in the progression rate ( $p = 0.349$ ). The results suggest that the recurrence rate is positively related to age, but the progression is not. It is recommended that patients who belong to the age group less than 40 years are expected to have smaller and singular tumours. Tumour recurrence is significantly lower in people of this age group, but the progression is not affected by age, and it is observed to be similar in all the age groups. This indicates to clinicians that early diagnosis and treatment can significantly lower the chance of recurrence in patients and improve the prognosis.<sup>13</sup>

A literature search revealed most data were extrapolated and analysed from EORTC trial and several other studies based on retrospective data analysis with low-level evidence. Few studies primarily looked at the incidence rate and disease progression after one year of treatment of low-risk low-grade bladder cancer.

SPSS (statistical package for social science), a data analysis software, was used to analyse the relationship between these variables. Tumour size is selected as a constant variable. With the help of Pearson's correlation, variables are tested, and the relation between them is found. Tumour size, mitomycin C instillation, recurrence and grade of differentiation are selected as a variable for the Pearson correlation test. Tumour size was selected as a continuous variable. A test run on SPSS shows that the weak negative relationship between age, tumour size, and recurrence indicates no true significance between these variables. The second test shows that tumour size, grade of differentiation, and recurrence have weak relation. The third correlation text indicates tumour size, Mitomycin C instillation, and recurrence have weak negative relation. After performing the test, it is found that these variables are related to each other.

Continued follow-up on low-risk bladder tumours would cost the trust thousands of pounds and generate a great burden on both NHS Trust hospitals and private sectors. However, in our opinion, recurrence of this disease, with or without progression, would not only have incurred a higher cost but would result in further consequences of hospitalization, procedures, and adjuvant therapy in addition to the effect on the overall patients' general health, performance and wellbeing. Hence, given the recurrence and progression beyond the 12 months in our group we felt that it would be inappropriate to further analyze the cost-effective saving from these check cystoscopies as keeping them cancer-free is the main objective and goal.

## CONCLUSION

Our initial review revealed a high likelihood of recurrence (33.9%) in the low-risk NMIBC patients after 12 months of being cancer free. It also demonstrated that there is further progression in 23.8%

of those with a later recurrence despite being asymptomatic. Therefore, we would recommend a 5-year follow-up surveillance and further up-to-date national collaboration to audit this patient subgroup to define a safe period of check cystoscopic follow-up for these patients and bring further robust evidence for NICE to build up their recommendations.

### ETHICAL APPROVAL

The ethics committee of the Trust has been sought and audit data collection has been facilitated by them. The University duly examined and approved this study before the commencing of the research

### LIMITATIONS OF THE STUDY

It is a retrospective observational study, the sample size is small, and data is collected from a single centre only. Fifteen patients missed follow-up during the study for different reasons.

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