NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of transurethral laser ablation for recurrent non-muscle-invasive bladder cancer

Non-muscle-invasive bladder cancer is present only in the lining of the bladder. It has not grown into the deeper muscle layer. In this procedure, a tube with a camera (cystoscope) is inserted into the bladder through the tube that carries urine out of the body from the bladder (urethra). A laser within the cystoscope is then used to destroy the cancer cells.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional

procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in December 2018 and updated in May 2019.

Procedure name

- Transurethral laser ablation for recurrent non-muscle-invasive bladder cancer.

Specialist societies

- British Association of Urological Surgeons (BAUS)
- Royal College of Surgeons
- Royal College of Surgeons of Edinburgh
- Royal College of Physicians and Surgeons of Glasgow.

Description of the procedure

Indications and current treatment

The most common form of bladder cancer is transitional cell carcinoma. Non-muscle-invasive transitional cell carcinoma is classified as stage Ta when it is confined to the uroepithelium with no spread into the bladder wall or beyond. It is classified as stage T1 when there is spread into the connective tissue layer between the urothelium and the muscle wall. Non-muscle-invasive transitional cell carcinomas usually appear as small growths from the bladder lining. They can be graded from G1 (low grade, least aggressive) to G3 (high grade, most aggressive). Carcinoma in situ consists of aggressive cancer cells that spread within the surface lining of the bladder and appear flat. It is more likely to recur after removal.

NICE's guideline on bladder cancer describes its diagnosis and management. Surgical interventions for non-muscle-invasive transitional cell carcinoma include transurethral resection, in which malignant tissue is removed with an electrocautery device during cystoscopy. Bacillus Calmette-Guérin (BCG) vaccine or chemotherapy drugs may be put directly into the bladder, either as treatments in themselves or as adjuvant therapy after transurethral resection. Cystectomy may also be necessary in some patients.

What the procedure involves

This procedure is most often used for very small, recurrent bladder tumours. It is usually done as day surgery using local anaesthesia. A flexible cystoscope is passed through the urethra into the bladder. The tumours are then ablated using a laser fibre contained in the cystoscope.

If there is a lot of bleeding after the procedure, a catheter may be inserted into the bladder.

Adjuvant intravesical chemotherapy may be offered to patients after the procedure.

The aim is to destroy the tumour with reduced morbidity compared with conventional treatments. The suggested benefits are less bleeding and reduced pain compared with cystodiathermy.

Outcome measures

Bladder cancer classification:

Tumour

<table>
<tr><td>Tx</td><td>No primary tumour can be evaluated</td><td rowspan="2"></td></tr>
<tr><td>T0</td><td>There is no evidence of a primary tumour in the bladder</td></tr>
<tr><td>Ta</td><td>Non-invasive papillary carcinoma</td><td rowspan="3">Non-muscle-invasive bladder cancer</td></tr>
<tr><td>Tis</td><td>Carcinoma in situ (CIS) or ‘flat tumour’. Cancer is only found on or near the surface of the bladder.</td></tr>
<tr><td>T1</td><td>The tumour has spread to the subepithelial connective tissue (lamina propria only)</td></tr>
<tr><td>≥T2</td><td colspan="2">Muscle-invasive bladder cancer</td></tr>
</table>

Grade

Grade 1 – the cancer cells look a lot like normal bladder cells. They are usually slow-growing and are less likely to spread.

Grade 2 – the cancer cells look more abnormal and grow slightly more quickly than grade 1 cancer.

Grade 3 – the cancer cells look very abnormal. They are more likely to grow more quickly.

Efficacy summary

Recurrence

In a case series of 109 patients (130 complete procedures), the total recurrence rate after laser ablation in the first 6 months was 20% (26/130). Of the 26 recurrences, 17 were at the treated location and 9 were at a different location.[1]

In a case series of 151 patients, the local recurrence rate after the first laser ablation procedure was 10% (median follow up of 24 months). In the multivariate analysis, the combination of tumour location at the ureteric orifice (odds ratio [OR] 5.3, p=0.004), increased size (OR 1.1, p=0.009) and age (OR 0.96, p<0.001) were statistically significantly associated with recurrence.[2]

In a case series of 59 patients, recurrence rate after laser ablation was 27% at 12-month follow up and 49% over the total study period (median follow up of 17 months); 3 patients had progression of tumour stage, grade or both.[6]

In a case series of 54 older frail patients with multiple comorbidities, recurrence at 3-month follow up was 11% for patients who had white light ablation and 4% for those who had laser ablation with photodynamic diagnosis. At 1-year follow up, the rates were 65% and 47% respectively.[5]

In a non-randomised comparative study of 41 patients (71 tumours), the local recurrence rate after laser ablation was 18% (13/71) and the recurrence rate in untreated areas of the bladder was 54% (38/71), with a mean follow up of 14 months; 49% (20/41) of patients were tumour free at follow up. In a subgroup analysis of 10 patients who had also had cystodiathermy before the study period, the local recurrence rate was less in the laser-treated group compared with cystodiathermy, but the difference was not statistically significant (p=0.39).[3]

In a case series of 21 patients who had laser ablation with a diode laser, the recurrence rate was 24% (5/21) with a median follow up of 14 months; all the recurrences were small (1 mm to 3 mm) and could be immediately biopsied and treated by laser. None of the patients had disease progression.[7]

In a non-randomised comparative study of 100 patients, the recurrence rate was 30% (15/50) for laser ablation and 36% (18/50) for transurethral resection.[8]

Patient satisfaction

In the case series of 109 patients, 85% (80/94) of patients reported that they were happy or very happy with the procedure, 12% (11/94) were satisfied, 1 was indifferent and 2% (2/94) were dissatisfied. All patients who completed a follow-up questionnaire answered that, if they had to have a new intervention, they would prefer laser coagulation to transurethral resection.[1]

In the case series of 151 patients, all patients were pleased with the procedure. In hindsight, 1 patient would have preferred a general anaesthetic procedure.[2]

In the non-randomised comparative study of 41 patients, all 33 patients who received a follow-up questionnaire returned it and were satisfied with their treatment; 6% (2/33) of patients said they would elect to have further procedures under general anaesthesia.[3]

In the case series of 54 patients, all patients said they would choose to have the procedure again.[5]

In the case series of 21 patients, all patients preferred to have outpatient laser treatment instead of inpatient transurethral resection of bladder tumours.[7]

Safety summary

Pain

The mean visual analogue scale (VAS) scores for pain were 2 (range 0 to 8) and 1 (range 0 to 7) respectively in the 2 case series of 109 and 151 patients.[1,2]

The VAS score for pain was 2 or less for 85% (28/33) of patients in the case series of 41 patients.[3]

Some pain was reported by 1 patient in a case series of 52 patients.[4]

A VAS pain score of 0 to 2 was reported by all patients in the case series of 54 patients.[5]

The median VAS pain score was 1 and 87% of patients reported a score of 3 or less in the case series of 59 patients.[6]

The median VAS pain score was 1 (range 0 to 7) in the case series of 21 patients.[7]

Haematuria

Haematuria was reported after 2% (2/130) of procedures in the case series of 109 patients; no treatment was needed.[1]

Haematuria was reported in 2% of patients in the case series of 151 patients; 1 patient who was taking warfarin had haematuria at day 7 after the procedure but the symptoms resolved after conservative management.[2]

Haematuria was reported in 1 patient in the case series of 54 patients; symptoms resolved spontaneously after 1 week.[5]

Haematuria needing hospital admission was reported in 1 patient in the case series of 59 patients.[6]

Minor haematuria for 24 hours was reported in 10% (2/21) of patients in the case series of 21 patients.[7]

Postoperative haematuria was reported in 6% (3/50) of patients who had laser treatment and 14% (7/50) of patients who had conventional transurethral resection in the non-randomised comparative study of 100 patients.[8]

Bleeding

Bleeding that needed intervention was reported in 1 patient in the case series of 52 patients (no further information provided).[4]

Infection

Acute epididymitis was reported in 1 patient 14 days after the procedure in the case series of 52 patients; the patient was admitted to hospital and had antibiotics.[4]

Dysuria or urinary frequency

Dysuria or increased urinary frequency that lasted 48 to 72 hours was reported in 23% of patients in the case series of 109 patients.[1]

Dysuria was reported in 4% of patients and frequency in 2% of patients in the case series of 151 patients.[2]

Dysuria without bacteriuria for up to 4 days was reported in 24% (5/21) of patients in the case series of 21 patients.[7]

Catheterisation

A urethral catheter was needed after the procedure by 1 patient in the case series of 52 patients (no further information provided).[4]

Catheterisation was needed in all patients who had conventional transurethral resection and 72% (36/50) of patients who had laser treatment in the non-randomised comparative study of 100 patients ($p<0.01$).The catheterisation time

was statistically significantly shorter in the laser treatment group (less than 24 hours in 54% (27) of patients who had laser treatment compared with 4% (2/50) of patients in the transurethral resection group, p<0.01).[8]

Bladder perforation

Bladder and jejunal perforation was reported in 1 patient described in a case report. The patient had previously had 2 transurethral resections and BCG treatment. She presented with intense hypogastric pain the day after intravesical Nd-YAG laser irradiation of a recurrent bladder tumour. Exploratory laparotomy revealed a perforation of a jejunal loop located in the pelvis and a small perforation in the peritoneum over the bladder. Resection of the perforated jejunal loop was done with primary anastomoses. The bladder was sutured and a Foley catheter was inserted. The catheter was removed after 7 days and the patient was discharged.[9]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers listed the following anecdotal adverse events: bleeding, infection, discomfort and disease progression. They considered that the following were theoretical adverse events: ablation of the tumour especially under local anaesthetic, may result in a higher recurrence rate that removing the tumour; it is usual not to biopsy when doing this procedure and there would be concern that tumour stage/grade progression may be missed.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to transurethral laser ablation for non-muscle-invasive bladder cancer. The following databases were searched, covering the period from their start to 2 April 2019: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published

studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded when no clinical outcomes were reported, or when the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with recurrent non-muscle-invasive bladder cancer.
Intervention/test	Transurethral laser ablation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 588 patients from 6 case series, 2 non-randomised comparative studies and 1 case report.[1–9]

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on transurethral laser ablation for recurrent non-muscle-invasive bladder cancer

Study 1 Planelles Gómez (2017)

Details

Study type	**Case series**
Country	Spain
Recruitment period	2013 to 2016
Study population and number	**n=109 (139 procedures)** **Patients with small recurrent non-muscle-invasive bladder tumours**
Age and sex	Mean 68 years (range 45 to 88); 80% (114/139) male
Patient selection criteria	Inclusion criteria: patients with low or intermediate risk of progression or recurrence, and patients with high risk of progression or recurrence but with a high surgical risk (ASA 4), with 5 or fewer lesions size 1.5 cm or smaller diagnosed by cystoscopy. Exclusion criteria: patients with a history of carcinoma in situ previous positive urine cytology, patients with high tumour risk and ASA 1 to 3, and those patients who did not wish to take part in the study.
Technique	Patients had treatment on an outpatient basis. A cystoscopy was done with a flexible cystoscope and a biopsy of cold-pinched lesions was collected. A holmium:YAG fibre laser was used through the flexible cystoscope, with an energy of 0.5 to 1 J/pulse and a frequency of 6 to 10 Hz. The fibre was kept about 2 mm away from the surface of the tumour until it had coagulated.
Follow up	**6 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Losses to follow up were not described. Patients were scheduled for a control cystoscopy at 3 months. Patients with recurrence had either photocoagulation or transurethral resection. Patients who did not have recurrence at 3 months were scheduled for another cystoscopic review 3 months later. Follow-up questionnaires were available for 72% (94/130) procedures.

Study design issues: Prospective, single-centre case series. The level of comfort during the procedure was assessed using a VAS (score 0 to 10). Patients were also asked to complete a urinary symptoms satisfaction questionnaire, which was collected at the 3-month follow-up visit.

Study population issues: Mean tumour size was 4 mm (range 2 to 15). Of the 130 completed procedures, 49 were low risk (38%), 64 were intermediate risk (49%) and 17 were high risk (13%).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **109** Of the 139 procedures that were done, 130 were completed (8 were changed to transurethral resection because of a high tumour burden or a difficult access site, and 1 procedure was interrupted by an anxiety crisis and the patient was rescheduled for transurethral resection under anaesthesia). Mean coagulation time=7 minutes (range 1 to 35) **Recurrence at 3-month follow up=16.9% (22/130)** • Number of recurrences at the same location=14 • Number of recurrences at a different location=8 • Low risk=5/22 • Intermediate risk=15/22 • High risk=2/22 **Recurrence at 6-month follow up=3.7% (4/108)** • Number of recurrences at the same location=3 • Number of recurrences at a different location=1 • Low risk=1/4 • Intermediate risk=3/4 • High risk=0/4 **Total recurrence rate in first 6 months=20%** **Level of satisfaction** • Very happy, n=49 • Happy, n=31 • Satisfied, n=11 • Indifferent, n=1 • Dissatisfied, n=2 100% (94/94) of patients who completed a questionnaire answered that if they had to have a new intervention, they would prefer laser coagulation to transurethral resection.	**Pain** Mean VAS score after the procedure=2 (range 0 to 8) **Intraoperative complications** • Haematuria=1.5% (2/130) (no treatment was needed and the procedure was completed) No patient needed catheterisation or subsequent hospital admission. Of the 89.1% of patients for whom a urine culture was available, asymptomatic bacteriuria was positive for 9.3%. 23% of patients reported dysuria or increased urinary frequency at home that lasted between 48 and 72 hours. No patients needed medical treatment for complications.
Abbreviations used: ASA, American Society of Anesthesiologists; VAS, visual analogue scale	

Study 2 Syed HA (2013)

Details

Study type	**Case series**
Country	UK
Recruitment period	2006 to 2011
Study population and number	**n=151 (259 procedures; 444 tumours)** **Patients with recurrent non-muscle-invasive bladder cancer**
Age and sex	Mean 73 years (range 49 to 99); 77% male
Patient selection criteria	Inclusion criteria: recurrence of non-muscle-invasive bladder cancer after primary transurethral resection of bladder tumours (grade 1 to 3, Ta-1), the ability to complete questionnaires and patients able to consent to treatment and follow up.
Technique	Patients had treatment on an outpatient basis. A holmium:YAG laser was used with a flexible cystoscope. Standard laser frequency was 6 Hz, with 0.9 kJ energy, but around more sensitive areas, such as the trigone, bladder neck and ureteric orifice area, the laser frequency was 6 Hz, with 0.6 kJ energy. Patients with a high risk of recurrence were offered a course of mitomycin. Biopsies were not routinely taken. The mean number of tumours treated per session was 1.7, with up to 6 tumours being treated in a single session.
Follow up	**Median 24 months (range 0 to 58)**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: 8 tumours were excluded from the analysis because of insufficient follow up.

Study design issues: Prospective case series. The primary outcome was local, on-site recurrence rates of non-muscle-invasive bladder cancer. Secondary outcome measures included off-site recurrence rates, complications, pain perception, and patient satisfaction.

Study population issues: Mean tumour size was 7.4 mm (range 2 to 40). 78% (116/151) of patients had stage Ta tumours and 22% (35/151) had stage T1 tumours. Eight patients were taking warfarin when they had the procedure.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **151**

Local recurrence rate for primary recurrence treatment=10%
Of those who developed local recurrence, 92% (22/24) had successful treatment with a further laser treatment; 2 patients needed a formal cystoscopy and diathermy under general anaesthesia.

An increased tumour size (9.5 mm compared with 7.1 mm) was an independent statistically significant risk factor for local tumour recurrence.

Recurrence rates by tumour location

	Tumour distribution (%)	On-site recurrence (%)
Ureteric orifice	5.8	19.4
Lateral wall	29.3	5.1
Bladder neck	4.7	4.0
Posterior wall	28.8	3.3
Dome	23.5	2.4
Trigone	7.7	2.4

Recurrence rates by grade and stage

	On-site recurrence (%)	Time to on-site recurrence, months (range)	Off-site recurrence (%)
Grade G1	3.4	15.8 (3 to 48)	47.0
Grade G2	7.4	9.0 (3 to 19)	30.0
Grade G3	12.0	12 (5 to 22)	32.0
Stage Ta	6.0	12.2 (3 to 48)	23.1
Stage T1	8.7	11.8 (3 to 21)	35.6
Overall			
G1 Ta	3.8	15.8 (3 to 48)	22.2
G2 Ta	4.4	8.0 (3 to 15)	18.9
G3 Ta	9.1	4.2	83.3
G1-2 T1	7.7	9.7 (3 to 19)	36.3
G3 T1	14.3	14.4 (3 to 21)	23.0

Median time to local recurrence=12 months
Median time to off-site recurrence=25 months

Multivariate binomial logistic regression model of recurrence

Variable	Beta	Significance level	Odds ratio	95% Confidence interval
Tumour location (ureteric orifice)	1.669	0.004	5.305	1.716 to 16.402
Tumour size (mm)	0.110	0.009	1.117	1.028 to 1.213
Age	-0.44	0.000	0.957	0.945 to 0.968

Patient satisfaction
100% of patients were pleased with the procedure. In hindsight, 1 of the patients would have preferred a general anaesthetic procedure.

Safety

Complications

- Dysuria=4.2%
- Frequency=1.5%
- Haematuria=1.9%

There were no documented microbiological urinary tract infections. There were no episodes of haemorrhage needing transfusion and no cases of bladder perforation.

One patient who was taking warfarin had haematuria at 7 days after the procedure. His symptoms resolved with conservative management.

The mean visual pain score was 1 (range 0 to 7).

Study 3 Syed HA (2001)

Details

Study type	**Non-randomised comparative study**
Country	UK
Recruitment period	1994 to 1997
Study population and number	**n=41 (52 treatments, 71 tumours)** (a subgroup of 10 patients (19 tumours) had also had cystodiathermy before 1994) **Patients with recurrent non-muscle-invasive bladder cancer**
Age and sex	Mean 67 years (range 47 to 87); 68% (28/41) male
Patient selection criteria	Patients with recurrent, previously documented low-grade, non-muscle-invasive transitional cell carcinoma less than 1 cm. Exclusion criteria: patients with their first tumour or those with high-grade or invasive disease.
Technique	Patients had treatment as day cases and the procedure was done using local anaesthesia. Holmium laser (Versapulse, Coherent Medical Group, US) was used during flexible cystoscopy. The laser fibre was held 2 to 3 mm away from the tissue, and a pulse of laser energy was fired at the target. If the effect was minimal, the tumours were treated in a contact mode or the power was increased. The tumour was treated first and, after visible shrinkage, the base was also treated. The mean total energy used was 0.48 kJ (5 to 10 Hz frequency and energy settings of 0.5 to 1.0 J/pulse). 10 patients had also previously had cystodiathermy.
Follow up	**Mean 14 months (range 3 to 33)**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: The follow-up questionnaire was only sent to the 33 patients who had had treatment within the previous 18 months. All 33 patients returned their questionnaires.

Study design issues: Small case series with retrospective analysis of a subgroup of 10 patients who had also had cystodiathermy before the study period. Patient satisfaction was assessed using a retrospective questionnaire.

Study population issues: Most patients (35/41) had grade II tumours; 6 patients had grade I tumours.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **41** **Local recurrence during study period=18% (13/71)** **Recurrence in untreated area of bladder=53.5% (38/71)** **48.8% (20/41) of patients were tumour free at follow up** **Subgroup analysis of 10 patients who historically had cystodiathermy** Of the 19 tumours treated by cystodiathermy before the study period, there were 6 (31.6%) local recurrences and 8 recurrences in the untreated area. In the laser group, 21 tumours were treated and there were 2 (9.5%) local recurrences and 5 out-of-field recurrences. The local recurrence rate was less in the laser-treated group compared with cystodiathermy, but the difference was not statistically significant (p=0.39). All 33 patients who received a follow-up questionnaire returned it and were satisfied with their treatment. 6.1% (2/33) of patients would elect to have further procedures under general anaesthesia.	There were no intraoperative or delayed complications. **Pain visual analogue scale score (n=33)** 84.8% (28/33) of patients rated their pain as 2 or less on a scale of 0 to 10.

Study 4 Jønler M (2004)

Details

Study type	**Case series**
Country	Denmark
Recruitment period	Not reported
Study population and number	**n=52** (88 procedures, 197 tumours) **Patients with recurrent papillary tumours of the bladder**
Age and sex	Median 72 years (range 51 to 87); 77% (40/52) male
Patient selection criteria	Patients with recurrent bladder tumours who had non-muscle-invasive bladder cancer (Ta) low-grade tumours.
Technique	The procedure was done under local anaesthesia alone and all patients had treatment as day cases. A holmium:YAG laser (Omnipulse, Trimedyne, US) was used through a flexible cystoscope. The standard setting was 40 W, a repetition rate of 40, with a single pulse using a single fibre of 0.2 to 0.4 mm. The settings were changed during the procedure if desired. The red aiming spot of the distal tip of the laser fibre was held a few millimetres from the tumour. If the tumour was clearly coagulated the base of the tumour was also treated. If not, the tumour was vaporised in contact mode, possibly with a higher setting.
Follow up	**4 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: No losses to follow up were described.

Study design issues: Small case series of consecutive patients. The main aim of the study was to assess patient satisfaction, complications and cost-effectiveness.

Study population issues: The median number of tumours per patient was 2 (range 1 to 8). The median size of the largest tumour was 5 mm (range 2 to 30). As the surgeons became more familiar with the laser technique, patients with larger or more tumours were scheduled for treatment with the laser rather than the standard transurethral resection of bladder tumours under anaesthesia.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **52 (88 procedures, 197 tumours)** Laser vaporisation=100% (197/197) Total median operative duration=15 minutes (range 2 to 30) All patients reported that they would have laser ablation again rather than a standard transurethral resection of bladder tumours under anaesthesia of a Ta papilloma recurred. The 5 surgeons rated the procedure as easy in 78% (68/88) of patients and acceptable in 16% (14/88). It was difficult in 3% (3/88) and very difficult in 3% (3/88).	**Pain during the procedure** In 86% (76/88) of procedures, patients had no pain. Discomfort was reported after 13% (11/88) of procedures and 1 patient reported some pain. None of the procedures was stopped because of pain. **Complications** • 1 patient needed a urethral catheter after the procedure* • 1 patient had bleeding that needed intervention* • 1 patient developed acute epididymitis 14 days after the procedure. The patient was admitted to hospital and had antibiotics. *No further information given – these were listed in a table, the text states that none of the patients had major bleeding or needed a catheter afterward.

Study 5 Wong KA (2013)

Details

Study type	**Case series**
Country	UK
Recruitment period	2008 to 2011
Study population and number	**n=54** (74 procedures) **Older frail patients and patients with multiple comorbidities, with small-volume recurrent non-muscle-invasive bladder tumours**
Age and sex	Mean 77 years (range 52 to 95); male:female ratio was 1.39:1
Patient selection criteria	Older frail patients and patients with multiple comorbidities, for whom general anaesthesia would present a high risk, and small-volume recurrent non-muscle-invasive bladder tumours. Exclusion criteria: first presentation of tumour, young age (under 50 years), large tumours (over 3 cm), tumours adjacent to the bladder neck when the patient is fit for treatment with curative intent, and untreated urinary infection.
Technique	Laser ablation was done in the outpatient department. A flexible cystoscope was used to map the bladder with white light. A holmium:YAG laser (Olympus KeyMed Ltd., UK) with a 365- or 200-nm fibre at 0.6 to 0.8Js energy and rate of 10 to 15 Hz was used to ablate the tumours. A subgroup of patients had PDD before laser ablation. In these patients, 50 ml hexaminolevulinate acid was instilled into the bladder 1 hour before the procedure. Patients were asked to void before the procedure and a PDD-enabled flexible cystoscope was used to visualise the bladder initially with white light, then blue light. Any additional tumours seen under blue light were noted before laser ablation was done.
Follow up	**1 year**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: No losses to follow up were described.

Study design issues: Prospective single-centre cohort study. The aims of the study were to evaluate the safety, tolerability and effectiveness of outpatient laser ablation, with and without PDD, of non-muscle-invasive bladder cancer in an older population.

Study population issues: More than half the patients had more than 3 comorbidities. Previous tumour histology ranged from G1pTa to T3 (1 patient had T3 disease, which was refractory to intravesical chemotherapy and radical treatment was not suitable; he had low-volume recurrence). Eight patients were taking warfarin at the beginning of the study; 4 stopped taking it before the procedure and 4 continued taking it. All patients had previous experience of inpatient cystoscopy under general anaesthetic.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **54** Additional tumours were seen in 21% of patients with PDD that were not seen with white light. **Recurrence** • 3-month follow up=10.6% (4.3% for patients who had laser ablation with PDD) • 1-year follow up=65.1% (46.9% for patients who had laser ablation with PDD) **Patient satisfaction** All patients would choose to have the procedure again. Patients noted that particular benefits were minimal pain and bleeding. **Markov modelling analysis – 10-year period** Outpatient laser ablation was more effective than inpatient cystodiathermy (3.68 compared with 3.56 quality-adjusted life-years).	**Pain during the procedure** All patients reported a pain score of 0 to 2 (on a visual analogue scale of 0 to 10). **Complications** 1 patient had haematuria for 1 week after the procedure, which resolved spontaneously. There were no other reported complications, including pain, haematuria, retention, urinary tract infections, or hospital admissions.
Abbreviation used: PDD, photodynamic diagnosis	

Study 6 Rivero Guerra A (2018)

Details

Study type	**Case series**
Country	Spain
Recruitment period	2009 to 2016
Study population and number	**n=59 (79 procedures)** **Patients with recurrence of non-muscle-invasive bladder cancer (small papillary tumours)**
Age and sex	Mean 66 years (range 45 to 86); sex not reported
Patient selection criteria	Prior papillary neoformation of low grade and stage (TaG1-2), size 10 mm or smaller, 5 or fewer tumours, negative cytology, low-grade recurrence in the opinion of the endoscopist, no demonstrated allergy to lidocaine.
Technique	All procedures were done on an outpatient basis. A 365 nm holmium laser fibre, with energy of 0.5 to 1 J and frequency between 5 and 10 pulses (maximum power 10 W) was inserted through a flexible cystoscope and fulguration of the tumours was done from the periphery to the base. Mitomycin C was then instilled into the bladder for at least 60 minutes.
Follow up	**Median 17 months (range 2 to 65)**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: After the procedure, a first cystoscopy and urinary cytology was done at 3-month follow up. Further follow ups were done 6-monthly until 2 years and then annually. No losses to follow up were described.

Study design issues: Prospective, single-centre cohort study. The aims of the study were to evaluate the efficacy, safety, and feasibility of holmium laser fulguration, in an outpatient setting, of selected tumours in patients with a history of low-risk bladder tumours.

Study population issues: 80% (47/59) of patients had TaG1 tumours diagnosed in the previous transurethral resection, 17% (10/59) had TaG2 tumours, 1 patient had atypical cystitis and 1 had focal hyperplasia. The median time from previous transurethral resection to fulguration was 27 months (range 4 to 148). 56% (33/59) of patients had previous treatment with mitomycin C instillations and 3% (2/59) had previous BCG instillations.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **59** **Recurrence=49.4% of procedures (27.3% at 12 months)** After the recurrence, 13 patients needed a traditional transurethral resection; 3 presented progression (either of stage, grade, or both). Progression to a muscle-infiltrating bladder tumour was not observed. In 2 of these patients, progression was after a second fulguration. **Time to recurrence (median)** • After treatment of first tumour=56 months • After treatment of a second tumour=10 months p<0.0001 **Time to recurrence (median)** • People who smoke=25 months • People who do not smoke=28 months p=0.389	**Pain during the procedure** Median pain score=1 (on a visual analogue scale of 0 to 10). 87.2% of patients had a score of 3 or less. **Complications** 1 patient needed hospital admission because of haematuria.

Study 7 Hermann G (2018)

Details

Study type	**Case series**
Country	Denmark
Recruitment period	Not reported
Study population and number	**n=21** **Patients with recurrent low-grade intermediate-risk bladder tumours**
Age and sex	Median 66 years (range 52 to 89); sex not reported.
Patient selection criteria	Inclusion criteria: recurrent Ta low-grade urothelial bladder tumour, tumour size not larger than 1.5 cm, and no more than 15 tumours in the bladder. Exclusion criteria: ongoing use of anticoagulants and macroscopic haematuria, pregnancy or breastfeeding, expected poor compliance, and age less than 18 years.
Technique	Fluorescence-guided diode laser destruction of bladder tumours. Hexaminolevulinate (Hexvix, Photocure, Norway) and lidocaine anaesthetic were instilled into the bladder through a catheter. Ibuprofen and acetaminophen were also offered as oral pain treatment. One hour later, laser destruction was done using a flexible videocystoscope and blue light, with a diode laser (Leonardo Laser, Biolitec Biomedical Technology, Germany). The laser power was set at 8 to 15 W, with a pulse duration of 10 milliseconds at 10 millisecond intervals. It was intended not to have contact between the fibre tip and the target. Patients had adjuvant intravesical chemotherapy instillations, according to guidelines.
Follow up	**Median 14 months (range 12 to 16)**
Conflict of interest/source of funding	The Foundation Juchum supported the study with a grant for a part-time medical doctor. Photocure ASA, Norway, supported the study by providing Hexvix for blue-light cystoscopy and a grant for nursing assistance. One author has provided services as a speaker in meetings funded by Photocure.

Analysis

Follow-up issues: All patients had follow-up cystoscopy and biopsy 1 month after the procedure.

Study design issues: Small, prospective, single-centre case series. Pain experienced during the procedure was measured on a VAS from 0 to 10. Symptoms were assessed using the European Organisation for Research and Treatment of Cancer QLQ-NMIBC24. This has a symptom score for lower urinary tract symptoms and a 'worry' score for concerns about the future course of the disease, both range 0 to 100 with higher scores indicating worse symptoms or worry. The pain VAS was completed immediately after the laser procedure, whereas the QLQ-NMIBC24 was completed on day 7. After the follow-up cystoscopy, patients were asked whether they preferred the inpatient or outpatient procedure for future tumour recurrences.

Study population issues: All patients had recurrent tumours and had previous inpatient transurethral resection of bladder tumours. Patients had a median of 3 recurrent tumours each (range 1 to 12), size 5 to 15 mm.

Other issues: The authors noted that primary tumours should not be treated with laser destruction.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **21** Median duration of cystoscopic examination and laser treatment was 29 min (range 19 to 45 min). **Median QLQ-NMIBC24 scores at 7-day follow up** • Symptoms=24 (range 0 to 67) • Worry=42 (range 0 to 100) At 1 month, cystoscopy, 10% (2/21) of patients had remnant flat low-grade dysplasia. **Recurrence=24% (5/21)** These were Ta low-grade recurrences, which were small (1 to 3 mm) and could be immediately biopsied and treated by laser. No patients had disease progression. During the laser procedure, photodynamic diagnosis identified tumours that were not seen on white light in 4 patients (19%). All patients preferred to have outpatient laser treatment instead of inpatient transurethral resection of bladder tumours.	Median VAS pain score during the laser procedure=1.0 (range 0 to 7; only 1 patient recorded level 7) • Minor haematuria for 24 hours=10% (2/21) • Dysuria without bacteriuria for up to 4 days=24% (5/21) None of these symptoms needed treatment; no urinary infections were recorded.
Abbreviations used: QLQ-NMIBC24, Quality of Life Questionnaire for Non-Muscle-Invasive Bladder Cancer; VAS, visual analogue scale.	

Study 8 Muraro G (2005)

Details

Study type	**Non-randomised comparative study**
Country	Italy
Recruitment period	Not reported
Study population and number	**n=100 (50 laser ablation, 50 transurethral resection)** Patients with non-muscle-invasive bladder cancer and comorbidities
Age and sex	Laser treatment group: mean 64.5 years (range 45 to 89), 78% male Transurethral resection group: mean 65.7 years (range 47 to 91); 80% male
Patient selection criteria	Not reported
Technique	Laser ablation: A holmium: YAG laser was used (Coherent Medical Group, US) with a small rigid cystoscope and sedation. The tip of the laser fibre was set at less than 2 mm from the base of the tumour or directly in contact with the tissue. It delivered 1 to 1.4 Joule of energy with a rate of 10 Hz to 15 Hz at 20-Watt power. A vaporisation technique was used to treat small tumours in which a fulguration type of effect was needed by placing the fibre at a distance of 2 to 3 mm from the tissue and doing the coagulation at 0.4 mm maximum depth. Transurethral resection was done using spinal anaesthesia and a rigid resectoscope.
Follow up	**3 years**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: Follow up was done every 3 months by urine cytology and cystoscopy. Losses to follow up were not described.

Study design issues: Retrospective non-randomised comparative study.

Study population issues: 95% of patients had high anaesthesiological risk (American Society of Anesthesiologists III or IV) and comorbidities such as hypertension (65%), chronic respiratory disease (40%), diabetes (30%), senile decay (10%), and varicose veins (8%). Most patients had tumours that were grade G1 (48%) or G2 (45%) and stage pTa (89%). There were no statistically significant differences in tumour stage and grade between the 2 treatment groups.

Other issues: It is not clear from the paper whether any patients had recurrent bladder tumours.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 100 (50 versus 50)

Postoperative hospital stay
<table>
<tr><th></th><th>Laser</th><th>Transurethral resection</th><th>P value</th></tr>
<tr><td>24 to 48 hours</td><td>38 (76%)</td><td>3 (6%)</td><td><0.01</td></tr>
<tr><td>72 hours</td><td>7 (14%)</td><td>27 (54%)</td><td></td></tr>
<tr><td>>96 hours</td><td>5 (10%)</td><td>20 (40%)</td><td></td></tr>
</table>
Recurrences

Laser=30% (15/50)
Transurethral resection=36% (18/50)

In the laser group, 10 recurrences were in the first year, 4 in the second year and 1 after 24 months of follow up. An increase in grade (G2 to G3) was seen in 12% (6/50) patients and 14% (7/50) showed progression in stage (3 pTa to pT1 and 4 pT1 to pT2).

In the transurethral resection group, 11 were in the first year, 5 in the second year and 2 in the third year of follow up. 8% (4/50) had an increase in grade (G2 to G3) and progression was seen in 14% (7/50) of patients (4pTa to pT1 and 3pT1 to pT2).
</td><td>
There were no perioperative complications.
Postoperative complications (24 to 48 hours)

Laser=6% (3/50) (haematuria on second postoperative day)
Transurethral resection=20% (10/50) (7 patients who were taking anticoagulant and antihypertensive treatment had haematuria)

p=0.04

Catheterisation
<table>
<tr><th></th><th>Laser</th><th>Transurethral resection</th><th>P value</th></tr>
<tr><td>No catheterisation</td><td>14 (28%)</td><td>0</td><td><0.01</td></tr>
<tr><td colspan="4">Postoperative catheterisation time</td></tr>
<tr><td><24 hours</td><td>27 (54%)</td><td>2 (4%)</td><td><0.01</td></tr>
<tr><td>48 to 96 hours</td><td>4 (8%)</td><td>33 (66%)</td><td></td></tr>
<tr><td>>96 hours</td><td>5 (10%)</td><td>15 (30%)</td><td></td></tr>
</table>
</td></tr>
</table>

Study 9 Ruiz-Tovar J (2008)

Details

Study type	**Case report**
Country	Spain
Recruitment period	Not reported
Study population and number	**n=1** **Patient with bladder and jejunal perforation after Nd-YAG laser irradiation of a recurrent bladder tumour**
Age and sex	76-year-old woman
Patient selection criteria	Not applicable
Technique	Intravesical Nd-YAG laser irradiation of a recurrent bladder tumour (35 W for 2 seconds)
Follow up	**Not reported**
Conflict of interest/source of funding	Not reported

Key efficacy and safety findings

Jejunal and bladder perforation after intravesical Nd-YAG laser irradiation of a recurrent bladder tumour

The patient presented with intense hypogastric pain the day after she had had intravesical Nd-YAG laser irradiation of a recurrent bladder tumour. A CT scan showed pneumoperitoneum and an air bubble inside the bladder wall. Exploratory laparotomy revealed a perforation of a jejunal loop located in the pelvis and a small perforation in the peritoneum over the bladder. Resection of the perforated jejunal loop was done with primary anastomoses. The bladder was sutured and a Foley catheter was inserted. The catheter was removed after 7 days and the patient was discharged.

The authors note that the patient had 2 previous transurethral resections and BCG treatment.

Validity and generalisability of the studies

- No randomised controlled trials were identified.
- There are different types of laser used for the procedure. Most of the evidence used a holmium laser and 1 study used a diode laser.[7] The case report of a perforation was related to the use of a Nd-YAG laser.[9]
- Two studies used photodynamic diagnosis (blue-light ablation) in some or all the patients.[5,7]
- Inclusion criteria for studies differed about size, stage and grade of bladder tumours.
- One study only included older frail patients with multiple comorbidities.[5]
- The evidence includes patients from Europe and the UK.

Existing assessments of this procedure

Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and CIS) were published by the European Association of Urology in 2017.[10] With regard to office-based fulguration and laser vaporisation, they state:

'In patients with a history of small, TaLG/G1 tumours, fulguration of small papillary recurrences on an outpatient basis can reduce the therapeutic burden and is a treatment option (LE: 3). There are no prospective comparative studies assessing the oncological outcomes.

Potassium titanyl-phosphate (KTP) laser vaporisation is associated with a low risk of complications.

Its oncologic outcomes need to be confirmed in a larger patient population.'

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

IP overview: Transurethral laser ablation for recurrent non-muscle-invasive bladder cancer

- Intravesical microwave hyperthermia and chemotherapy for non-muscle-invasive bladder cancer. NICE interventional procedures guidance 628 (2018). Available from http://www.nice.org.uk/guidance/IPG628
- Laparoscopic cystectomy. NICE interventional procedures guidance 287 (2009). Available from http://www.nice.org.uk/guidance/IPG287
- Electrically-stimulated intravesical chemotherapy for superficial bladder cancer. NICE interventional procedures guidance 277 (2008). Available from http://www.nice.org.uk/guidance/IPG277

NICE guidelines

- Bladder cancer: diagnosis and management. NICE guideline 2 (2015). Available from http://www.nice.org.uk/guidance/NG2

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by specialist advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Two specialist adviser questionnaires for transurethral laser ablation for non-muscle-invasive bladder cancer were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 5 companies who manufacture a potentially relevant device for use in this procedure. NICE received 2 completed

submissions. These were considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- Ongoing trials:
  - Outpatient PDD Guided Laser Mediated Destruction of Bladder Tumors (LaserIII) (NCT02886026); RCT; Denmark; estimated enrolment 248; estimated study completion date February 2019.
- Evidence was only included if the study specified that patients were having treatment for small recurrent non-muscle-invasive bladder cancer. En-bloc resections were not included.

References

1. Planelles Gomez J, Olmos Sanchez L, Cardosa Benet JJ et al. (2017) Holmium YAG Photocoagulation: Safe and Economical Alternative to Transurethral Resection in Small Nonmuscle-Invasive Bladder Tumors. Journal of Endourology 31: 674–8
2. Syed HA, Talbot N, Abbas A et al. (2013) Flexible cystoscopy and Holmium:Yttrium aluminum garnet laser ablation for recurrent nonmuscle invasive bladder carcinoma under local anesthesia. Journal of Endourology 27: 886–91
3. Syed HA, Biyani CS, Bryan N et al. (2001) Holmium:YAG laser treatment of recurrent superficial bladder carcinoma: initial clinical experience. Journal of Endourology 15: 625–7
4. Jonler M, Lund L, Bisballe S (2004) Holmium:YAG laser vaporization of recurrent papillary tumours of the bladder under local anaesthesia. BJU International 94: 322–5
5. Wong KA, Zisengwe G, Athanasiou T et al. (2013) Outpatient laser ablation of non-muscle-invasive bladder cancer: is it safe, tolerable and cost-effective? BJU International 112: 561–7
6. Rivero Guerra A, Fernandez Aparicio T, Barcelo Bayonas I et al. (2018) Outpatient Holmium laser fulguration: A safe procedure for treatment of recurrence of nonmuscle invasive bladder cancer. Actas Urologicas Espanolas 42: 309–15
7. Hermann GG, Morgensen K, Rosthoj S (2018) Outpatient diode laser treatment of intermediate-risk non-invasive bladder tumors without sedation: efficacy, safety and economic analysis. Scandinavian Journal of Urology DOI: 10.1080/21681805.2018.1450782
8. Muraro GB, Grifoni R, Spazzafumo L (2005) Endoscopic therapy of superficial bladder cancer in high-risk patients: Holmium laser versus transurethral resection. Surgical Technology International (14) 222–6
9. Ruiz-Tovar J, Gonzalez R, Conde S et al. (2008) Jejunal and bladder perforation: complication of intravesical Nd-YAG laser irradiation of bladder tumour. Acta Chirurgica Belgica 108: 595–6
10. Babjuk M, Burger M, Compérat E et al. (2017) EAU Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and CIS). European Association of Urology. Available from: https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Non-muscle-Invasive-BC_TaT1-2017.pdf [accessed 15/01/2019]

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	02/04/2019	Issue 4 of 12, April 2019
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	02/04/2019	Issue 4 of 12, April 2019
HTA database (CRD website)	02/04/2019	n/a
MEDLINE (Ovid)	02/04/2019	1946 to April 01, 2019
MEDLINE In-Process (Ovid)	02/04/2019	1946 to April 01, 2019
MEDLINE Epubs ahead of print (Ovid)	02/04/2019	April 01, 2019
EMBASE (Ovid)	02/04/2019	April 01, 2019

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Urinary Bladder Neoplasms/
2	Carcinoma, Transitional Cell/
3	((bladder* or urinary or urothelial* or transitional) adj4 (Neoplasm* or Cancer* or Carcinom* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or lesion* or Masses* or Sarcom* or Metastas*)).tw.

4	(NMIBC or NMIBT).tw.
5	or/1-4
6	Laser Therapy/ or Lasers/ or Lasers, Solid-State/ or Lasers, Semiconductor/
7	((laser* or light* or photo*) adj4 (diode* or holmium or thallium or solid-state or vapor* or vapour* or destroy* or destruct* or therap* or enucleat* or ablat* or treat* or technique*)).tw.
8	"transurethral laser*".tw.
9	TULA.tw.
10	or/6-9
11	5 and 10
12	Animals/ not Humans/
13	11 not 12
14	limit 13 to english language

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow up	Direction of conclusions	Reasons for non-inclusion in table 2
Beer M, Jocham D, Beer A et al. (1989) Adjuvant laser treatment of bladder cancer: 8 years' experience with the Nd-YAG laser 1064 nm. British Journal of Urology 63:476-8	Case series n=252 procedures FU=12 months	Recurrence rate for laser treatment of recurrent tumours=54% in stage A and 75% in stage B. Small tumours (less than 0.5 cm) can be treated effectively by laser therapy alone, under local anaesthesia and without the need for catheter drainage and hospitalisation.	Study population is a mixture of patients with primary or recurrent tumours and a mixture of tumour stages and grades.
Beisland HO and Seland PA (1986) prospective randomized study on neodymium-YAG laser irradiation versus TUR in the treatment of urinary bladder cancer. Scandinavian Journal of Urology & Nephrology 20: 209-12	RCT n=122 (84 with primary tumours) FU=2 years	Neodymium-YAG laser irradiation is a safe and efficient treatment of bladder tumours of stage T-1 and superior to transurethral resection (TUR) except in very small tumours which can be completely removed in one piece without resecting into tumour tissue. In muscle-invasive tumours of stage T-2, combined treatment with TUR and laser irradiation is superior to TUR alone. Occurrence of new tumours in non-treated areas is independent of treatment modality.	Study population is a mixture of patients with primary or recurrent tumours and includes muscle-invasive bladder cancer.
Cano-Garcia MC, Fernandez-Aparicio T, Hidalgo Agullo G et al. (2016) Outpatient holmium laser treatment for recurrent low-grade superficial bladder cancer under local anesthesia. Minerva Urologica e Nefrologica 68: 204-8	Case series n=37 FU=median 13 months	All patients had scores on the VAS of 3 or less. There was 1 patient with haematuria, who needed hospitalisation. After a median follow up of 13 months, there was a 35.1% recurrence rate with 1 case of tumour progression.	Studies with more patients or longer follow up are included.
Gao X, Ren S, Xu C et al. (2008) Thulium laser resection via a flexible cystoscope for recurrent non-muscle-invasive bladder cancer: initial clinical experience. BJU International 102: 1115-8	Case series n=32 FU=12 months	The accumulated recurrence rates at 3, 6 and 12 months were 9%, 22% and 28%, respectively.	Studies with more patients or longer follow up are included.
Greskovich FJ 3rd and von Eschenbach AC (1991) Bladder perforation resulting from the use of the neodymium:YAG laser.	Case report n=1	**Bladder perforation after Neodymium: YAG laser ablation** Patient had TUR of a bladder tumour, which was a grade II, invasive papillary transitional cell	Case report of a safety event that is already described in table 2.

Lasers in Surgery & Medicine 11: 5-7		carcinoma, external beam radiation of the bladder, mitomycin C treatment, a right radical nephroureterectomy with diverticulectomy, excision of a bladder cuff, laser ablation, TUR of an ulcer in the high posterior wall (during which the bladder was perforated). After developing recurrent bladder tumour he had treatment with laser fulguration. The next day he had abdominal pain and an intraperitoneal bladder perforation was identified. This was successfully treated with catheter drainage for 17 days.	
Hossain MZ, Khan SA, Salam MA et al. (2005) Holmium YAG laser treatment of superficial bladder carcinoma. Mymensingh Medical Journal: MMJ 14:13-5	Case series n=30 (18 recurrent) FU=6 to 12 months	No recurrence was found during the 6- to 12-month follow-up period. The procedure was found safe, effective, and acceptable.	Studies with more patients or longer follow up are included.
Johnson DE (1994) Use of the holmium:YAG (Ho:YAG) laser for treatment of superficial bladder carcinoma. Lasers in Surgery & Medicine 14: 213-8	Case series n=15 FU=3 months	No intraoperative or delayed complications occurred. At the 3-month follow-up cystoscopy, 4 patients (27%) were without disease; 8 patients (53%) had out-of-field recurrences; and 3 patients (20%) were classified as having in-field recurrences.	Studies with more patients or longer follow up are included.
Kourambas J, Delvecchio F C, Preminger GM (2001) Low-power holmium laser for the management of urinary tract calculi, structures, and tumors. Journal of Endourology 15: 529-32	Case series n=80 FU=3 months	Complete tumour ablation was attained in 70%, with a tumour-free rate of 60% at 3 months.	Mixed indications.
Kramer MW, Bach T, Wolters M et al. (2011) Current evidence for transurethral laser therapy of non-muscle-invasive bladder cancer. World Journal of Urology 29: 433-42	Review 18 articles n=650	Today, Nd:YAG does not play any role in treatment of lower urinary tract transitional cell carcinoma. Ho:YAG and Tm:YAG seem to offer alternatives in the treatment of bladder cancer, but still to prove their potential in larger prospective randomised controlled studies with long-term follow up.	No meta-analysis. The review also includes studies describing en-bloc resections.
Kramer MW, Wolters M, Cash H et al. (2015) Current evidence of transurethral Ho:YAG and Tm:YAG treatment of bladder cancer: update 2014. World Journal of Urology 33: 571-9	Review 18 articles n=800	Tumour vaporisation seems to be a promising alternative for the treatment of recurrent tumours in selected patients. It can be performed in an office-based approach without the need of general anaesthesia. The use of photodynamic diagnostic might enhance surgical quality.	No meta-analysis. The review also includes studies describing en-bloc resections.

Soler-Martinez J, Vozmediano-Chicharro R, Morales-Jimenez P et al. (2007) Holmium laser treatment for low grade, low stage, non-invasive bladder cancer with local anesthesia and early instillation of mitomycin C. Journal of Urology 178: 2337-9	Case series n=36 FU=12 months	The incidence of recurrence at 12 months was 25%, mainly in the first 15 cases. Laser photocoagulation with local anaesthesia and sedation is easy to perform and well tolerated. There were no complications and the recurrence rate was similar to that of TUR, as calculated using the recurrence calculator of the 2006 guidelines on TaT1 (non-musical-invasive) bladder cancer from the European Association of Urology.	Studies with more patients or longer follow up are included.