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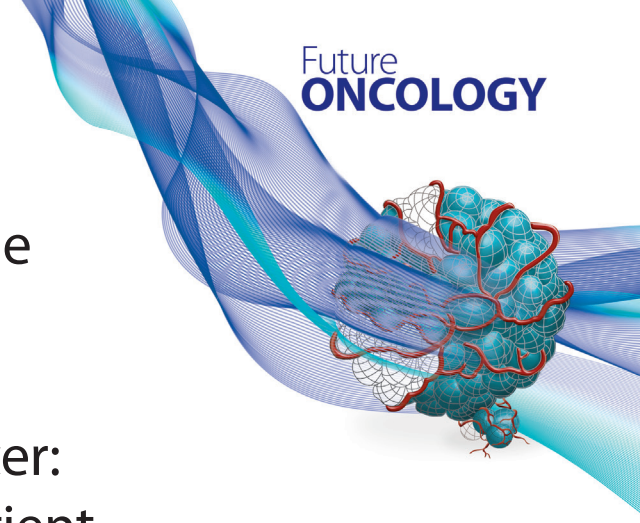

RESEARCH ARTICLE

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Hexaminolevulinate hydrochloride blue-light flexible cystoscopy in the detection and follow-up of nonmuscle-invasive bladder cancer: cost consequences during outpatient surveillance in Sweden

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Aim: This study explored the cost consequences of introducing hexaminolevulinate hydrochloride-guided blue-light flexible cystoscopy (HAL BLFC) as an adjunct to white-light flexible cystoscopy compared with white-light flexible cystoscopy alone, for the detection and management of nonmuscle invasive bladder cancer in Sweden. **Methods:** The model evaluated 231 patients in the outpatient setting after successful initial transurethral resection of the bladder tumor. **Results:** HAL BLFC introduction across all risk groups resulted in minimal budget impact (+1.6% total cost/5 years, or 189 Swedish Krona [SEK] per patient/year), and translated to cost savings in intermediate- and high-risk groups from year 2. **Conclusion:** HAL BLFC allowed more outpatient treatment with improved recurrence detection and reduced transurethral resection of the bladder tumors, cystectomies, bed days and operating room time, with minimal cost impact across all risk groups, demonstrating the economic benefits of introducing HAL.

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KEYWORDS
• bladder cancer • budget impact • cost-consequences model • detection • economic evaluation • fluorescence cystoscopy • fulguration • hexaminolevulinate • recurrence • Sweden

Bladder cancer is the most common malignancy of the urinary tract and is the seventh most common cancer in Sweden [1]; bladder cancer accounts for approximately 330,000 new cases and 130,000 deaths per year worldwide [2]. Although bladder cancer is up to three-times more common in men than in women, approximately 60,000 women worldwide are diagnosed with the disease every year [2], and relatively more women die from the disease than men. Like many solid tumors, bladder cancer incidence increases with age. Tumors of the bladder rarely occur before the age of 40 to 50 years, and arise most commonly in the seventh decade of life. Approximately 2400 new cases and 600 deaths are reported annually from bladder cancer in Sweden [3], with an estimated prevalence of 21,000 people (as of 31 December 2009).

The majority of bladder cancers are diagnosed as nonmuscle-invasive bladder cancer (NMIBC), but recurrence rates may be as high as 70% [4]. A key goal in NMIBC treatment is the successful identification and removal of cancerous tumors to prevent recurrence to invasive disease in order to enhance survival [5]. Of those patients diagnosed with carcinoma *in situ* (CIS), approximately half will progress to muscle-invasive bladder cancer (MIBC) if left untreated [1]. The primary treatment

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of NMIBC is transurethral resection of the bladder tumor (TURBT; **Figure 1**) [1,3], though the limitations associated with using white-light cystoscopy (WLC) to identify the location and extent of multiple cancerous lesions often mean patients who undergo TURBT are still at risk of recurrence due to overlooked tumors [6].

Hexaminolevulinate hydrochloride (HAL; Hexvix®, Photocure ASA, Norway) is a photosensitizer approved for use in Sweden with blue-light cystoscopy as an adjunct to standard WLC for the detection and treatment of patients with bladder cancer. HAL is selectively taken up and metabolized by malignant cells, leading the cells to fluoresce when subjected to blue light [7]. Several studies have established that using HAL with blue light improves clinical outcomes of such procedures, including increased detection and resection of tumors, leading to a reduction in recurrence and an improvement in the

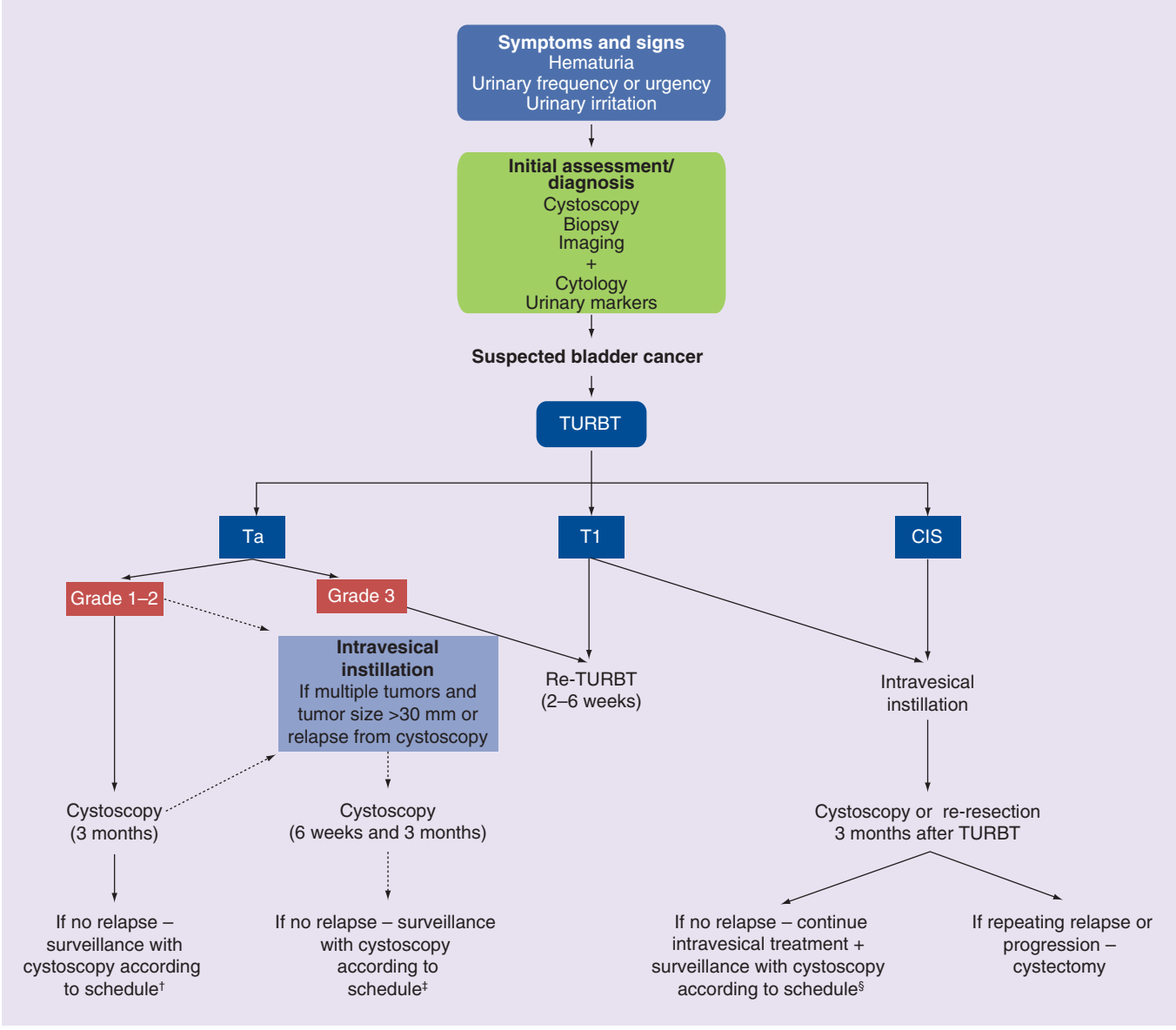

Figure 1. Patient management flow diagram based on Swedish guidelines for bladder cancer.

†Second cystoscopy after 9 additional months, then annually up to 5 years.

‡Third cystoscopy every 6 months for 2 years, then annually up to 10 years.

§Cystoscopy + cytology every 3 months for 2 years, then every 6 month up to 5 years, and then annually.

CIS: Carcinoma *in situ*; TURBT: Transurethral resection of the bladder tumor.

overall management of patients with bladder cancer [4,7–9]. As a result, the use of HAL is recommended in the European Association of Urology (EAU) guidelines [10], and a European expert panel has recommended the use of HAL blue-light cystoscopy during initial TURBT and for the follow-up of intermediate- and high-risk patients, citing both the clinical and cost–effectiveness of this tool in the management of NMIBC [6]. In addition to the randomized clinical trials, observational studies have recently been published confirming the beneficial outcomes of adding HAL blue light in a real practice setting [11–13].

Bladder cancer is one of the most costly malignancies to manage from diagnosis to death due to high long-term survival in NMIBC with frequent intensive, routine monitoring and treatment [4–5,14]. A recent study reported the budget impact of introducing the incorporation of a single installation of HAL blue-light cystoscopy for TURBT in Sweden, using a decision tree model based on the EAU guidelines [15]. While the clinical and economic benefits of using HAL blue-light cystoscopy during TURBT have been demonstrated, the cost consequences of introducing HAL blue-light flexible cystoscopy (BLFC) in an outpatient (OP) setting as an adjunct to white-light flexible cystoscopy (WLFC) in Sweden are unknown. Therefore, a cost-consequences model was developed to assess the economic impact of using HAL BLFC compared with using WLFC alone, in the detection of cancerous lesions during OP surveillance in patients diagnosed with NMIBC in Sweden.

Methods

• Patient population

The population included in the current model were patients undergoing surveillance throughout regular follow-up appointments in an OP setting after being diagnosed with NMIBC and successfully treated with a TURBT in an operating room (OR) setting. The patients were then stratified into risk groups according to low-risk, intermediate-risk or high-risk subgroups (see **Supplementary Table 1** [1,16–18]). All patients who entered the model were therefore successfully treated as true positives in risk of a recurrence of NMIBC or progression to MIBC.

The number of patients was based on information given by clinical advisors who estimated that an average-size clinic had approximately 200–250 patients included in the surveillance setting. Based on a prevalence of 0.231% [19], it was assumed that the population size in an average-size clinic was 100,000, yielding a total of 231 patients entering the model.

Based on Swedish guidelines [3], the follow-up schedule was set-up for the following patient subgroups as:

- Low risk: at 3 months, 12 months and then annually for the remainder of the time horizon
- Intermediate risk: at 3 months, 9 months, bi-annually for 2 years, and then annually for the remainder of the time horizon
- High risk: at every 3 month for 2 years, and then bi-annually for the remainder of the time horizon

• Model structure

The model combines a decision tree and a Markov cohort state transition model structures, which was informed by the literature review and by expert clinical opinions. Patient history was captured in the model by allowing patients who experienced a recurrence to be treated accordingly. These patients have a different follow-up schedule, risk of recurrence and risk of progression depending on when the recurrence took place.

A schematic depicting the model structure is presented in **Figure 2** and summary of the base case key model characteristics are shown in **Table 1**. Patients in a higher-risk group could not return to a lower-risk group than where they entered the model; patients could either remain in the same risk group or move to a higher risk group and it was possible for patients to experience a recurrence during any cycle of the model. Depending on the current risk group and cycle, patients would transition through an identical pathway as they did at model entry.

In the model, each risk group consisted of four possible health states depending on detection, each of which could progress to MIBC, yielding a total of 13 health states (3 risk groups × 4 detection states + 1 progression state). Progression was an absorbing health state that was independent of previous health states.

• Model health states

All patients entered the model as true negatives (i.e., no tumor) into one of three mutually exclusive health states based on their risk group stratification. It was assumed that all patients had successfully been treated prior to entering

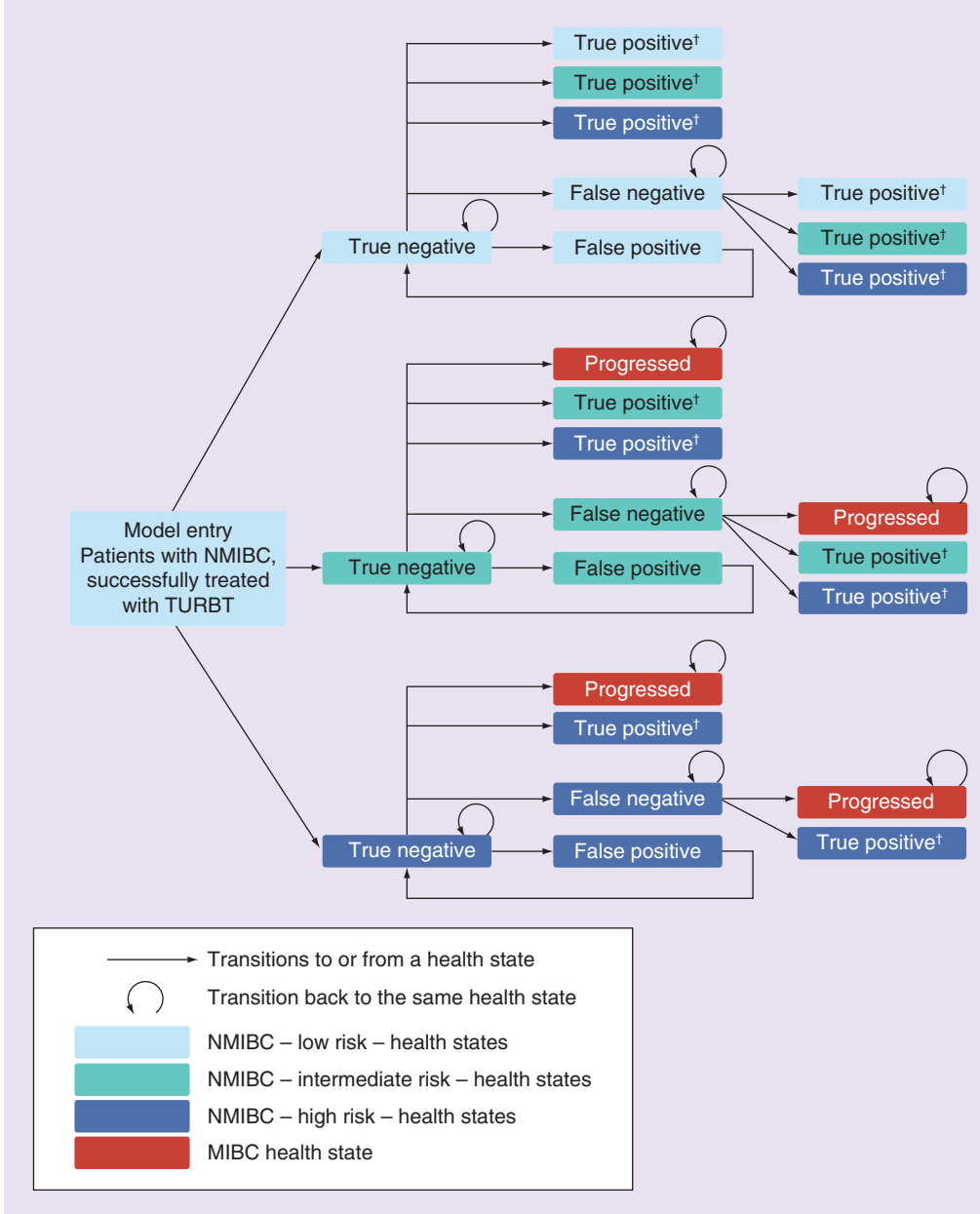

Figure 2. Overview of the model structure.
†Patients change Markov trace as at model entry, based on the current cycle and risk group. The follow-up schedule starts over accordingly.
MIBC: Muscle-invasive bladder cancer; NMIBC: Nonmuscle-invasive bladder cancer; TURBT: Transurethral resection of the bladder tumor.

the model and that no cost or consequences were added during model entry. The first cycle in the model was the first follow-up visit that occurred at 3 months after a TURBT for all risk groups.

If a follow-up visit was scheduled, patients could transition into any of the five detection health states, namely true negatives (no tumor), false positives (nonrecurrence detected as a recurrence), true positives (detected recurrence), false negatives (recurrence of NMIBC missed during follow-up) and progressed (progressed to MIBC; all-absorbing state from which patients could not transition further in the model).

The follow-up schedule in the base case setting was strictly setup according to EAU and Swedish guidelines as shown above.

• Treatments

Patients in the intervention arm received HAL BLFC as an adjunct to WLFC during follow-up visits within the first year according to the treatment schedule defined in the Swedish guidelines **(Figure 1)** [3]; however, patients with a low risk of recurrence did not receive HAL BLFC at the 12-month follow-up visit. Patients received WLFC alone at all other follow-up visits. All patients in the WLFC arm received WLFC alone during all follow-up visits.

• Model inputs

A Kaplan–Meier timetable of recurrence and progression by risk group was sourced from the study by Millán-Rodriguez and colleagues presented in **Tables 2 & 3**. From these, the annual probabilities of recurrence and progression were derived (see **Supplementary Table 2**). No extrapolation was necessary as the study covered a 5-year period.

In the absence of available data, an assumption was made using the most up-to-date systematic review of the diagnostic test performance of HAL rigid cystoscopy in a study by Burger and colleagues (sensitivity of 94.8% for HAL BLFC and 80.4% for WLFC) [24], and the positive predictive value was estimated with the help of the Swedish clinical advisers (91.0 and 92.0% for HAL BLFC and WLFC, respectively).

Patients that had a recurrence but were missed during the follow-up visit (i.e., false negatives) had an increased risk of changing NMIBC risk group or progression to MIBC compared with

Table 1. Summary of the key model characteristics (base case).

Aspect	Details
Model type	Cost-consequence model
Analytical method	A combination of decision tree and Markov cohort state transitions
Model perspective	Purchaser (hospitals and other healthcare providers)
Model population	Patients in the outpatient surveillance setting after being diagnosed with NMIBC and receiving a TURBT in an inpatient setting
Time horizon	5 years
Cycle length	3 months
Country setting	Sweden
Discount rate	3% for costs
Treatment arms within executable model	HAL BLFC adjunct to WLFC WLFC alone
Health outcomes	Total costs (discounted) over 5 years Disaggregated costs after 5 years (discounted) Number of flexible cystoscopies over 5 years Number of rigid cystoscopies w/o TURBT over 5 years Number of rigid cystoscopies with TURBT over 5 years Number of cystectomies over 5 years Bed days Outpatient and operating room time used over 5 years Urologist time used over 5 years Nursing time used over 5 years Patient distributions at end of model (model validation)
Patient subgroups in the surveillance population	Low-risk patients (15%) Intermediate-risk patients (45%) High-risk patients (40%)
Uncertainty	Deterministic sensitivity analysis Scenario analysis
Scenario analysis	Scenario 1: only low-risk patients enter the model Scenario 2: only intermediate-risk patients enter the model Scenario 3: only high-risk patients enter the model Scenario 4: only high-risk patients enter the model and 18.75% of the high-risk patients (75% of CIS [25%][†]) receive fulguration in OP when detected using HAL BLFC

[†]It was assumed that 25% of high-risk patients have CIS.
BLFC: Blue-light flexible cystoscopy; CIS: Carcinoma in situ; HAL: Hexaminolevulinate hydrochloride; NMIBC: Nonmuscle invasive bladder cancer; OP: Outpatient; TURBT; Transurethral resection of bladder tumor; WLFC: White-light flexible cystoscopy.

Table 2. Kaplan–Meier timetable, cost inputs and annual probability timetable of recurrence and progression presented in the original study by Millán-Rodriguez *et al.*

Time	Recurrence			Progression		
	Low	*Intermediate*	*High*	*Low*	*Intermediate*	*High*
Year 1	15.0%	26.0%	39.0%	0.0%	0.4%	8.0%
Year 2	25.0%	39.0%	50.0%	0.0%	1.2%	13.0%
Year 3	30.0%	45.0%	56.0%	0.0%	1.8%	16.0%
Year 4	38.0%	50.0%	58.0%	0.0%	2.6%	17.0%
Year 5	45.0%	53.0%	61.0%	0.0%	2.6%	19.0%

Data taken from [16].

those recurrences that were detected and treated accordingly (i.e., true positives; relative risk: 2.56; see **Supplementary Information**) [16].

The relative risk of recurrence using fulguration was incorporated in the model under the assumption that using WL alone during fulguration had the same effect as using WL-assisted TURBT, while using HAL BLFC during fulguration reduced the risk of recurrence after 1 year by a third (relative risk = 0.65 for low-, intermediate- and high-risk patient groups) based on expert input.

As fulguration with WLFC was assumed to have the same effect as TURBT (WLC), the same relative risk was used in the model. A similar assumption was made in a recently published study by Al Hussein Al Awamlh *et al.*, where the recurrence rate did not differ between office-based fulguration (WLFC) and OR-based TURBT (WLC) [25]. All patients in the low-risk group received fulguration, while no high-risk patients received fulguration and fulgurations were performed in 40 and 25% of patients receiving HAL BLFC and WLFC alone, respectively.

Patients that progress to MIBC were to be followed-up with CT imaging for the remainder of the time horizon. Furthermore, it was assumed that patients could have a local tumor recurrence or metastatic recurrence after progression to MIBC and being treated with cystectomy. The risk of recurrence was derived from the EAU guidelines, which provided metastatic-free recurrence rates and survival-free recurrence rates at 1, 3 and 5 years after cystectomy [1,26]. The values used in the model for year 1, 3 and 5 for local tumor recurrence were 15, 28 and 30%, while those for metastatic recurrence were 36, 56 and 66%, all respectively [1,26]. These values were applied using tunnel states as they were time-dependent recurrences.

Adverse events (AEs) were not included in the model as no clinically relevant AEs were connected to either WLFC or HAL BLFC in an OP setting. This was in-line with previous modeling practice in the area. Although inclusion of AEs resulting from TURBT and cystectomy could have been feasible in theory, this was not done as they would have had negligible impact on the incremental results, which was also in-line with the literature [17].

Mortality was not accounted for in the current model since the excess mortality due to NMIBC was again negligible [17]. Additionally, since the time horizon was only 5 years, deaths due to progression to MIBC would be low. The incremental difference between the comparators would therefore have been very minor and would have unnecessarily introduced further complexity to the model without adding significant benefits.

All costs in the model were sourced as indicated in **Tables 2 & 3**.

The number of bed days for cystectomy was sourced from the official statistics related to the diagnose-related code (DRG) code for cystectomy in the model (M05C) for 2013 in Sweden. On average in Sweden, a cystectomy required 8.81 bed days [27].

The definition of TURBT in the model is a surgical day case DRG procedure (M15O); however, a fraction of the procedures would require inpatient stay. Two DRGs for TURBT inpatients stay M15E (not complicated) and M15C (complicated) were available where the average care days are presented [27]. The average duration of bed days of across TURBTs was derived by weighting the three average durations with the number of times each of these DRGs were reported in year 2013 (1.59 days).

• Scenario & subgroup analyzes

A total of four scenarios were analyzed to provide the results per risk group to determine the sensitivity of the model: only low-risk patients at the model start (Scenario 1), only intermediate-risk

patients at the model start (Scenario 2), only high-risk patients at the model start (Scenario 3) and only high-risk patients at model start where 18.75% of the high-risk patients (75% of CIS [25%]) received fulguration in OP when detected using HAL BLFC (Scenario 4).

Results

• Cost consequences

In the base case, all costs and consequences are presented in 2014 Swedish Kronas (SEKs; 10 SEK = €1.12, US$1.28 or GBP£0.82) for the total 231 patients in the base case perspective. The total discounted costs per year over 5 years and the disaggregated discounted cost at 5 years are presented in **Tables 4 & 5**, respectively. The total costs of using HAL at prespecified follow-ups and WLFC alone over 5 years were SEK 14,033,864 and SEK 13,815,155, respectively **(Table 4)**. The estimated total budget impact of the intervention was 1.6% (SEK 218,709) over the comparator, which represented a budget impact of SEK 947 (SEK 218,709 divided by 231 patients) for an average patient over 5 years, or 189 SEK per patient per year. As can be seen in **Table 4**, the higher cost was only prevalent in the first year whereas it decreased in a longer time perspective from year 2 onward.

The major cost driver, accounting for the highest total cost, was the treatment of MIBC (cystectomy, chemotherapy and surveillance after progression), followed by the cost of staff and facilities for flexible cystoscopies in the surveillance setting, followed by treatment of high-risk recurrences (BCG; **Table 5**). The majority of the cost difference from using HAL BLFC was attributed to the extra time needed (staff and facility) to perform the flexible cystoscopy in the intervention treatment arm. The majority of cost savings came from the avoided treatment of MIBC (chemotherapy and costs after progression); this was likely the cost savings that could be observed in years 3–5 in **Table 4**, as the early identification of patients and TURBT treatment lowered the risk of patients progressing to MIBC. It was assumed that the cost of HAL would be covered by the payer; therefore this cost did not impact the overall cost.

Table 3. Cost inputs to the model.

Model parameter	Cost per procedure (2014 SEK†)		Ref.
	WLFC + HAL BLFC	*WLFC*	
Cost of cystoscopy equipment in OP setting	492,000.00	412,000.00	KARL STORZ (2014)
Cost of diagnosis in OP setting	1580.00	917.00	Inputs from a hospital perspective estimated based on clinical expert opinion
Cost of diagnosis + fulguration/biopsy in OP setting	2130.00	1467.00	Unit costs of operating room (SEK10,000), outpatient visit room (SEK2,000), urologist or anesthesiologist (SEK1400) and nurse (SEK1000) per hour
Cost of TURBT	10,600.00		
Cost of cystectomy	79,000.00		Time required conducting respective procedure and the additional time required using HAL
BCG therapy (6 weekly instillations and maintenance schedule of 3 months over 2 years)	18,900.00‡		Medac cost [20]
Immediate chemotherapy instillation (one dose)	1070.50‡		Drug injection [21] Mitomycin cost [20]
Adjuvant chemotherapy instillation (six doses)	3651.50‡		
Neoadjuvant cystectomy chemotherapy	4510.50‡		Drug injection [21] Treatment dosing [22] MVDC cost [20]
Imaging for MI surveillance	2803.50‡		Pelvis, abdomen, chest CT scan [23]
Local tumor recurrence	4510.50‡		Assumed same as 'neoadjuvant cystectomy chemotherapy'
Metastatic recurrence	52,628.61‡		3-month palliative care with consultation, therapy and medication [20,21]

†10 SEK = €1.12, US$1.28 or GBP£0.82.
‡The cost for the hospital was assumed to be 50% of the DRG and drug costs to only cover the overhead and staff costs (in-line with the other costs).
BCG: Bacillus Calmette–Guérin; BLFC: Blue-light flexible cystoscopy; HAL: Hexaminolevulinate hydrochloride; MVDC: Methotrexate, Vinblastine, Doxorubicin, Cisplatin; OP: Outpatient; SEK: Swedish Krona; TURBT: Transurethral resection of bladder tumors; WLFC: White-light flexible cystoscopy.
Data taken from [16].

Table 4. Total costs (discounted) over 5 years in the base case setting and in the scenario analyzes (in 2014 Swedish Kronas[†]).

Outcome	HAL BLFC	WLFC alone	Difference (% Δ)
Base case analysis			
Year 1	5,139,424	4,738,885	400,538
Year 2	3,391,898	3,474,751	-82,854
Year 3	2,181,173	2,230,304	-49,131
Year 4	1,763,850	1,796,192	-32,342
Year 5	1,557,519	1,575,022	-17,503
Total	14,033,864	13,815,155	218,709 (1.6%)
Scenario analyzes			
Total (only low-risk patients enter the model)	2,276,060	2,033,769	242,290 (11.9%)
Total (only intermediate-risk patients enter the model)	6,423,778	6,316,619	107,159 (1.7%)
Total (only high-risk patients enter the model)	27,002,005	26,669,028	332,977 (1.2%)
Total (high-risk patients only, where 18.75% of the high-risk patients [or 75% of the CIS patients] are treated with fulguration instead of TURBT upon recurrence with HAL BLFC)	25,792,927	26,669,028	- 876,101 (-3.3%)

[†]10 Swedish Kronas = €1.12, US$1.28 or GBP£0.82.

BLFC: Blue-light flexible cystoscopy; CIS: Carcinoma in situ; HAL: Hexaminolevulinate hydrochloride; TURBT: Transurethral resection of bladder tumors; WLFC: White-light flexible cystoscopy.

• Procedures

Flexible cystoscopies

The total cost of flexible cystoscopy was found to be slightly higher for HAL BLFC (0.2% increase over 5 years). While the number of flexible cystoscopies was higher for HAL BLFC, the difference in the number of procedures between arms was minimal **(Supplementary Table 3)**. HAL BLFC has more follow-ups early on due to an increased detection of recurrence, and the timing of follow-up visits was not synchronized between treatment arms at year 3. In reality, the number of visits will be comparable between the arms throughout the 5-year time horizon; however, in a longer time horizon, HAL BLFC is anticipated to have more visits as fewer patients will progress to MIBC and thus will continue to undergo surveillance. The higher cost observed for flexible cystoscopies with HAL BLFC was attributed to the extra time needed for staff and facility to perform HAL BLFC as an adjunct to WLFC, rather than the extra visits observed.

Rigid cystoscopies

The number of rigid cystoscopies with TURBT decreased by a total of 3.7% over 5 years and HAL BLFC only had more TURBTs than WLFC alone in year 1. The higher number of TURBTs in the first year resulted from earlier identification of patients with NMIBC using HAL BLFC **(Supplementary Table 3)**.

Fulgurations

There was a 9.5% increase in the number of fulgurations over the 5-year time horizon with HAL BLFC compared with WLFC **(Supplementary Table 3)**. This increase was due to the fact that all patients in the low-risk group and 40% (HAL BLFC) or 25% (WLFC) of the patients in the intermediate-risk group received fulguration. Most patients who had a recurrence were in the high-risk group and as such did not receive any fulgurations in the base case model. The absolute change in the number of fulgurations was lower in magnitude than that of TURBTs (3.3 more fulgurations compared with 4.7 fewer TURBTs), meaning that in total, HAL BLFC led to fewer treatments of recurrences.

Cystectomies

HAL BLFC led to a reduction in cystectomies over 5 years (4.3%) and at each year of the time horizon compared with WLFC alone **(Supplementary Table 3)**. This result was due to the increased identification of NMIBC patients in the OP surveillance setting, thus reducing the number of false-negative patients, who had an increased risk of progression to MIBC.

• Detection of false-positive recurrences

HAL BLFC resulted in an 8.1% increase in the detection of false-positive recurrences over the 5-year time horizon **(Supplementary Table 4)**.

These patients incurred extra costs in terms of biopsies; however, the cost of such procedures was low in comparison to the additional true positives detected using HAL BLFC as an adjunct to WLFC.

• Resource use

HAL BLFC was estimated to lead to a 4.1% decrease in the number of bed days as fewer patients progressed to MIBC and experienced a cystectomy. In addition, fewer patients received very resource heavy treatments such as palliative care (**Supplementary Table 4**). HAL BLFC was also estimated to reduce OR time by 4.1% compared with WLFC over the 5-year time horizon due to fewer TURBTs and cystectomies being performed following the introduction of HAL BLFC.

• Scenario analyzes

Four scenario analyzes were performed to assess the cost consequences of introducing HAL BLFC in certain patient subgroups stratified by risk.

Scenario 1: In a scenario analysis, the model was set to only include low-risk patients at the start of the model. The total costs over 5 years were 11.9% higher for HAL BLFC in this risk group compared with WLFC alone and HAL BLFC was not cost saving at any point in time; the highest increase in cost with HAL BLFC was observed in year 1 of the model. Compared with the base case, the proportion of added costs of HAL BLFC versus WLFC alone was greater in this scenario; however, it should be noted that the overall total cost for this risk group was substantially lower compared with the base case. As such the incremental cost of SEK 259,791 (SEK 225 per patient per year) represented a much larger fraction of the total cost in this scenario, but the total incremental cost was comparable to that of the base case (SEK 218,709 or SEK 189 per patient per year; **Supplementary Tables 5 & 6**).

HAL BLFC led to a reduction in resource use across all types of procedures versus WLFC alone, both in the OP and OR. Although all recurrences were treated with fulguration in the low-risk group, some patients could have changed risk group upon recurrence and were therefore treated with TURBT. HAL BLFC led to both fewer fulgurations and TURBTs in total, which may have been attributed to a reduction in the risk of future recurrences for the patient associated with treating recurrent tumors with HAL BLFC. The intervention also led to a slight reduction in cystectomies and bed days; however, over 5 years, low-risk patients had <1 cystectomy and one bed day in each treatment arm, thus the percentage difference between treatment arms may be misleading.

Scenario 2: In an additional scenario that only included intermediate-risk patients at the start of the model, the total cost over 5 years was 1.7% higher for HAL BLFC in this risk group compared with WLFC alone (SEK 107,159 or SEK 93 per patient per year); however, the intervention became cost saving from year 2 to 5 and it is possible that this trend would have continued beyond the model time horizon. The results are more beneficial for the intervention than what

Table 5. Disaggregated costs (discounted) after 5 years in the base case setting (in 2014 Swedish Kronas[†]).

Cost item	HAL BLFC	WLFC alone	Difference (Δ)
Cost for staff and facility for WLFC	1,669,095	1,665,828	3,267
Extra time required for HAL	504,422	0	504,422
Biopsies and fulgurations in OP	19,531	17,746	1785
Cystoscopy equipment in OP	466,312	390,179	76,133
Rigid cystoscopies with TURBT	1,220,068	1,265,187	-45,118
BCG therapy	1,340,428	1,258,128	82,300
Chemotherapy instillation (mitomycin)	208,614	249,275	-40,661
Cystectomy	4,251,105	4,437,934	-186,829
Neoadjuvant chemotherapy	242,718	253,385	-10,667
Imaging for MI surveillance	2,500,870	2,600,119	- 99,249
Recurrence of progressed cancer	1,610,700	1,677,373	-66,673
Total	14,033,864	13,815,155	218,709 (1.6%)

[†]10 Swedish Krona = €1.12, US$1.28 or GBP£0.82.
BLFC: Blue-light flexible cystoscopy; HAL: Hexaminolevulinate hydrochloride; OP: Outpatient; TURBT: Transurethral resection of bladder tumors; WLFC: White-light flexible cystoscopy.

was seen in the base case scenario, but it should be noted that the total costs are lower in the intermediate-risk only scenario (Supplementary Tables 7 & 8).

HAL BLFC led to less resource use across all types of procedures, both in the OP and OR, versus WLFC alone except fulgurations, which were increased by 21.3%. In the scenario with only intermediate-risk patients, HAL BLFC led to a 14.5 and 7.8% reduction in TURBT and cystectomies, respectively, compared with WLFC alone. HAL BLFC also led to fewer bed days and OR time compared with WLFC alone (-11.2 and -11.6%, respectively). In the intermediate-risk group, the observed clinical impact may be a result of the assumption that more patients could receive fulguration instead of TURBT with HAL BLFC than with WLFC alone.

Scenario 3: In a scenario where only high-risk patients entered the model, the total cost over 5 years was 1.2% higher for HAL BLFC in this risk group versus WLFC alone; however, the intervention was cost saving from year 2 to 5 and it is possible that this trend would have continued after the model time horizon. The results of this scenario were more beneficial compared with the base case, where a 1.6% cost increase was observed. And although the absolute cost increase was larger, the incremental cost of SEK 332,977 (SEK 288 per patient per year) became a smaller fraction of the total costs than what it was in the base case (SEK 218,709 or SEK 189 per patient per year; Supplementary Tables 9 & 10).

The HAL BLFC led to a reduction in cystectomies, OR time and bed days. HAL BLFC also led to an increased detection of tumors; as such, the number of TURBTs increased versus WLFC alone. The reduction in cystectomies was mainly due to the improved detection and treatment of recurrences, as false negatives had an increased risk of progression until being treated.

Scenario 4: In a scenario where the model was set to only include high-risk patients at the start of the model where 18.75% of the high-risk patients (or 75% of the CIS patients) were treated with fulguration instead of TURBT when detected upon recurrence with HAL BLFC, the total cost over 5 years was 3.3% lower for HAL BLFC versus WLFC alone (Savings of SEK 876,101 or SEK 758 per patient per year). The total cost of the intervention was higher than the comparator in year 1, but HAL BLFC became cost saving from year 2 to 5, and it is possible that this trend would have continued after the model time horizon (Supplementary Tables 11 & 12).

The HAL BLFC led to a reduction in OR resource use, meaning that using HAL BLFC led to a 6.5% reduction in OR time (-58 h) and fewer bed days when used in this risk group under the circumstance that a fraction of the CIS patients were treated with fulguration if detected with HAL BLFC.

Discussion

The introduction of HAL BLFC as an adjunct to WLFC in the OP surveillance setting offers a number of patient, clinical and economic benefits over WLFC alone for patients with bladder cancer. Within this model, the introduction of HAL BLFC as an adjunct to WLFC identified more patients with NMIBC compared with WLFC alone, due to the improved detection. The early detection of recurrence is likely to lead to improved disease management which may improve patient clinical outcomes.

The improved early detection, combined with a reduction in the number of more invasive procedures, such as TURBT and cystectomies, is likely to translate into improved quality of life for patients with NMIBC. The introduction of HAL BLFC resulted in an overall reduction (-3.7%) in the number of rigid cystoscopies with TURBT performed, though in year 1 there were 1.7% more TURBTs, which was due to improved detection. The HAL BLFC also resulted in fewer false-negative patients when compared with WLFC alone, which decreased the risk of progression to MIBC and resulted in fewer cystectomies and people living with MIBC. The HAL BLFC was also estimated to reduce the number of bed days and OR time (both -4.1%). This reduction in resource use translates to increased availability for patients with other diseases, reducing the burden of bladder cancer on Swedish healthcare resources. As a result of earlier detection with HAL BLFC, fewer patients progressed to MIBC and had a cystectomy, and fewer patients received very resource-heavy treatments such as palliative care (Supplementary Table 5). By enabling more procedures to be performed in the OP setting, patients were able to recover in their homes rather than in the hospital, as demonstrated by the reduction in bed days.

In addition to patient and resource benefits, the introduction of HAL BLFC as an adjunct

to WLFC was cost-neutral over 5 years, with only a marginal 1.6% increase in total cost when compared with WLFC alone; moreover, despite higher costs in year 1, HAL BLFC was cost saving from year 2 onward. It is possible that a longer time horizon may result in total cost savings for HAL BLFC, although this would add more uncertainty to the model. The majority of the added costs of HAL BLFC came from the additional cost of flexible cystoscopies in the OP, and the majority of the cost savings came from fewer MIBC treatments and reduced patient progression following earlier detection.

This model is in agreement with two recently published cost–effectiveness studies in NMIBC [6,25], though this is one of the first models focused on the surveillance setting in NMIBC. A study by Al Hussein Al Awamlh *et al.* demonstrated that the use of office-based cystoscopy and fulguration was more cost-effective than TURBT for treating low-risk NMIBC, which resulted in cost savings over time and reduced disease burden [25]. The publication by Witjes and colleagues concluded that the addition of HAL BLC to WLC resulted in improved quality-adjusted life-years and was no more expensive than WLC alone at initial TURBT due to improved detection and tumor removal compared with WLC alone [6]. Similar to our study, the costs of HAL BLC reduced over time, and the authors attributed this to the reduced need for additional operations to treat disease recurrence [6].

In this model, the costs associated with HAL BLFC vary depending on the patient population modeled. In scenarios where either only low-risk patients or intermediate-risk patients entered the model, added costs were due to the extra time and equipment required to perform HAL BLFC in the OP **(Supplementary Tables 6 & 8)**, and in the case of only intermediate-risk patients, there were added costs of biopsies and fulgurations. Though costs were saved for all other cost items, the total overall cost savings did not exceed the total incremental cost over the 5-year time horizon in these risk groups. The slightly higher costs of biopsies and fulgurations in the intermediate-risk patient scenario were due to the assumption that more recurrences in the intermediate-risk group could have been treated in the OP when using HAL BLFC.

The costs of high-risk patients had the largest contribution to the base case scenario as demonstrated by the total costs presented in only low-risk (~SEK 2 million; SEK 1732 per patient per year), only intermediate-risk (~SEK 6 million; SEK 5195 per patient per year) and only high-risk (~SEK 27 million; SEK 23,377 per patient per year) patient scenarios. This result was expected, given that high-risk patients represented 40% of the model population in the base case and incurred higher costs **(Supplementary Tables 9 & 10)**. In a scenario where the model was set to only include high-risk patients at the start of the model and 18.75% of the high-risk patients (or 75% of the CIS patients) were treated with fulguration instead of TURBT upon recurrence with HAL BLFC, the use of fulguration in the OP for a fraction of the CIS patients in this risk group was cost saving over 5 years. The main benefits were likely a combination of the improved detection and treatment of recurrences (positive effect on false negatives and the increased risk of progression). In addition, a fraction of the patients were moved over to the OP for treatment with fulguration, which in turn had an effect on the future risk of recurrences as the tumor was removed while using HAL BLFC instead of WLFC alone.

Within the Markov model structure, patient history was added using tunnel states in which patients that experienced a tumor recurrence restarted the follow-up schedule accordingly and were at risk for another tumor recurrence. This approach was perceived to better represent clinical practice; however, it also underestimated the benefits of earlier tumor detection as costs could get accumulated early in the model, which was especially true for high-risk patients. As such, and to prevent patients from experiencing an endless loop with recurrence, high-risk patients were excluded from restarting the follow-up schedule within the first year of the model, though they still had a high risk of recurrence.

This model incorporated a number of assumptions. To adjust for the fact that the benefits of HAL BLFC may be underestimated when modeling the diagnostic performance, the model included a number of additional aspects. In the absence of a treatment effect, one assumption was to introduce the possibility to treat patients with fulguration in the OP setting, which in turn avoids TURBTs in the OR setting. It is assumed that HAL BLFC after fulguration leads to a 35% reduction in risk of recurrence compared with WLFC fulguration, and that 15% more patients with HAL BLFC get fulguration

compared with patients with WLFC, which was based on expert opinion. This assumption has not been reported in previous submissions and is based on estimates. Although it does not have a large impact on the overall outcome, since it is only applied to low risk and intermediate risk patients, it does move the results in the logical direction.

In addition, adjustments were introduced for false-negative patients that were missed during a follow-up visit. These adjustments impart the same reduction in risk of recurrence due to early detection using HAL BLFC as if a treatment effect was implemented in the model. False-negative patients had an increased risk of progressing to a more severe NMIBC or MIBC during the time they were not detected; however, these were not believed to make up for the additional costs that occurred due to a higher sensitivity of HAL BLFC, which led to more treatments of recurrences and reinitiating the follow-up schedule.

At the time of the model development, no data were available for the diagnostic test performance of HAL BLFC in the OP surveillance setting. Therefore, in the absence of available data, an assumption was made using the most up-to-date systematic review of the diagnostic test performance of HAL rigid cystoscopy. Also, the positive predictive value was not possible to estimate from the same source as the diagnostic test performance, and was estimated with the help of the Swedish clinical advisers and further supported by published data for rigid WLC [28].

Other imaging modalities such as narrow-band imaging or Storz professional imaging enhancement system are under evaluation. With consideration of acquisition price points and diagnostic accuracy, the current model could provide a preliminary look at their costs and consequences. Such an evaluation may be considered in the future.

Limitations

There are some limitations to this model that should be considered. Due to the complex pathway in the follow-up and recurrence of NMIBC, a patient-level simulation may have been an appropriate modeling approach in order to capture the benefits of HAL BLFC for patients; however, to date, no such data were available to perform such simulations and a cohort model was employed. The model did not take into account the fact that a high-risk patient with multiple recurrences could have a cystectomy before progression to MIBC. In addition, the relative difference in detection of HAL BLFC and WLFC was assumed to be the same as when used in rigid cystoscopy. The base case model did not take preparation time and recovery time into consideration (for example, patients staying in the hospital who are not in the OR), as these costs are difficult to estimate in monetary terms, they vary among hospitals, and they depend on standard practices.

Some core model inputs included assumptions based on the best available data or clinical opinion (risk group stratification, risk of recurrences, increased risk of progression for undetected recurrences, proportion of false negatives detected after being missed at follow-up); however, the sensitivity analysis showed that these had very little impact on the relative outcome of the model. In addition, the Millán-Rodríguez study was used to inform this model; however, no immediate postoperative chemotherapy installation was used in that study, which is recommended in the Swedish guidelines and may reduce the rates of recurrence and progression that were used in the model.

The clinical benefits of using HAL BLFC may not have been fully captured in the base case setting of the model as the objective of this model was to look at the detection of recurrences in the surveillance setting by excluding any relative differences in treatment effects, such as reduced recurrences after TURBT. All TURBT-treated patients in the model were assumed to use WLFC alone in order to isolate the impact of recurrence detection in surveillance; however, it is possible that improved detection during surveillance is directly linked to the treatment effect of TURBT in the OR. This feature could not be incorporated in the model due to a paucity of data as no causal relationship has been established.

Conclusion

The introduction of HAL BLFC as adjunct to WFLC results in minimal financial impact versus WLFC alone over 5 years, while improving patient clinical outcomes and reducing Swedish healthcare resource use. The main benefits of introducing HAL BLFC over the 5-year time horizon are observed in high-risk patients, but it is anticipated that using HAL BLFC in all risk groups will lead to more beneficial results over the long term. HAL BLFC is cost saving when treating high-risk patients where a fraction of the

CIS tumors are treated with fulguration. Patients are also likely to experience an improved quality of life with HAL BLFC as a result of earlier detection, reduced recurrence rates, and the avoidance of more invasive surgical procedures and hospitalization by undergoing treatment in the OP setting. The reduction in the number of TURBT and cystectomies with HAL BLFC versus WLFC alone further benefits hospitals by reducing OR time and bed days, allowing such resource to be used for other patients.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: http://www.futuremedicine.com/doi/full/10.2217/fon-2015-0021

Author contribution

All authors contributed to the design of this study and the writing of the manuscript.

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EXECUTIVE SUMMARY

- The hexaminolevulinate hydrochloride (HAL) blue-light flexible cystoscopy (BLFC) use in all risk groups results in a minimal financial impact for healthcare providers while adding benefits for patients and freeing up hospital resources.
- The use of HAL BLFC in low- and intermediate-risk patients leads to fewer follow-up visits, recurrences and transurethral resection of bladder tumors compared with white-light flexible cystoscopy alone.
- The HAL BLFC use in high-risk patients leads to earlier treatment, which reduces the number of cystectomies versus white-light flexible cystoscopy alone.
- The main cost savings with the use of HAL BLFC are in high-risk patients, although the savings occur from year 2 onward.
- The HAL BLFC is likely to be both cost saving and adding clinical benefits when used in high-risk (carcinoma *in situ*) patients, of whom a fraction are treated with fulguration.
- The HAL BLFC may improve patient quality of life as a result of earlier detection, reduced recurrence rates and avoidance of more invasive surgical procedures and hospitalization by undergoing treatment in the outpatient setting.

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