Academic Lecture on Intravesical BCG

9 September 2016

Catalpa Garden, Hotel Royal Macau

Cohosts:

Macau Urological Association

Japan BCG Laboratory

Main Life Corp., Ltd.

Chair:
Dr. Ian Lap Hong

President, Macau Urological Association

Consultant Urologist, Hospital Conde S. Januario

Speaker I:
Dr. Eddie Chan

Clinical Associate Professor (Honorary),

The Chinese University of Hong Kong

Consultant of Division of Urology,

Prince of Wales Hospital

Speaker II:
Dr. Eiji Kikuchi

Associate Professor,

Dept. of Urology, Keio University School of Medicine

Opening Note from the Chair
Dr. Ian Lap Hong, President of Macau Urological Association

Intravesical BCG has been used for a long time in Macau for the treatment of bladder cancer, however the history is a little complicated. Previously, Immucyst was in the market because OncoTICE stopped the production. Unfortunately however, three years ago, Immucyst supply also stopped, and through our Hong Kong colleagues we have had the opportunity to use Immunobladder from Japan.

Until now, we have had around ten to twenty patients who have used Immunobladder, and from our short early experience, we have found that the effect is quite strong but also the side effects. However having talked to Dr. Eddie and Dr. Eiji , their experience says otherwise, so today is a good opportunity to discuss and learn from these experts.

As you know, Dr. Eddie Chan is Associate Professor at the Hong Kong Chinese University and an expert in bladder cancer. He is now honorary secretary in the Hong Kong Urological Association, and a very important organizer of the future of the association.

Dr. Eiji Kikuchi is Associate Professor at the Department of Urology, Keio University School of Medicine, and an expert in the use of BCG. It is our honor today to have Dr. Eiji share his experience today.

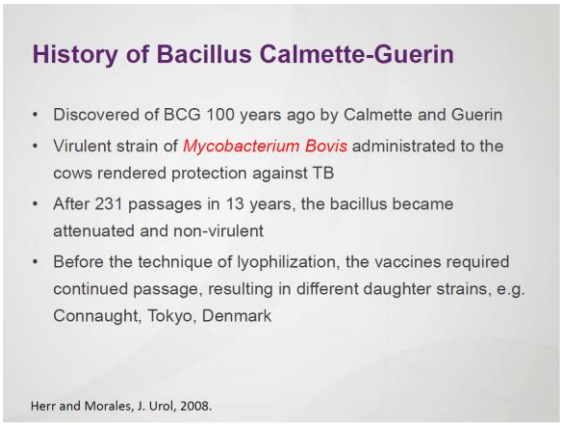
Dr. Eddie Chan

Complications of Intravesical BCG & their Management (HK Experience)

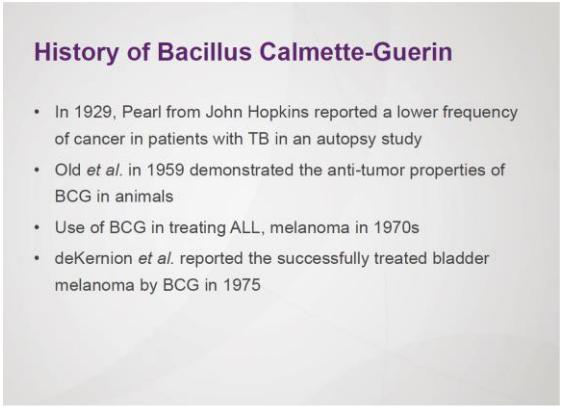
Slide 1

Fig. 1. Camille Guerin (left) and Albert Calmette (c 1921)

Figure 2



Slide 3



Slide 4

The focus of the seminar today is on the complications of BCG and their management. However, as Dr. Kikuchi will talk about this in detail, I will change the tone in my presentation to a more casual experience sharing. I will start by explaining a little on the background of BCG.

Historical background

BCG is so called because of these two guys, Calmette and Guérin [Figure 2] who discovered the bacteria 100 years ago. So it is a rather old thing. It is a *Mycobacterium bovis* —not a tuberculosis—and over 13 years, they subcultured it over many generations, and finally they found that it grows into a non-virulent attenuated strain. [Slide 3] This is the start of the BCG that is now used clinically.

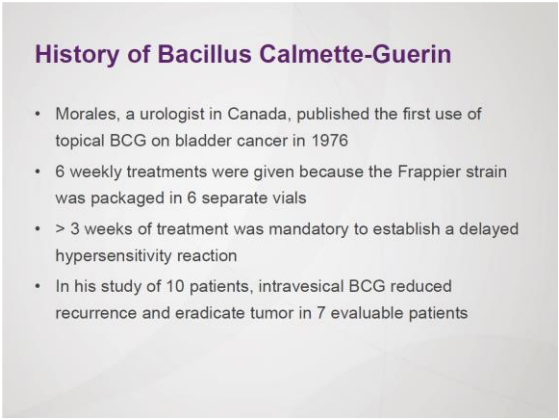
One thing you need to know is that there are many different strains of BCG: Connaught, Tokyo, Denmark, etc., but right now there is no clinical data on which strain is better or less potent, even though there are pre-clinical studies on the effectiveness of different strains on bladder cancer prevention.

In 1929, Pearl from Johns Hopkins first used BCG. Remember this is almost 100 years ago, a time when drug of choice if rather limited. [Slide 4] You almost want to give any kind of drug to the patient when they have cancer - If you think that it may help, and you would give it in the hope that hopefully tomorrow the patients can survive, no matter from the disease or from your drugs.

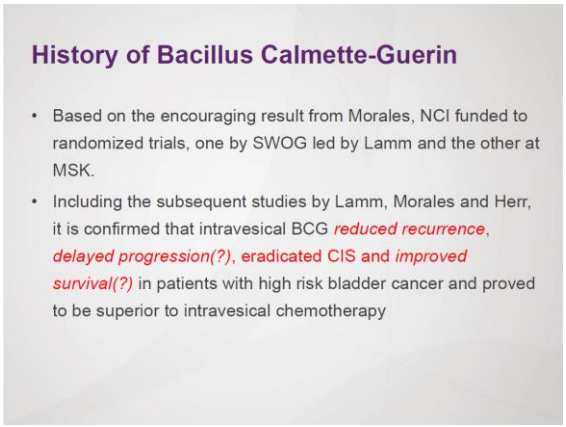
In the 1950s, it was found in animals that BCG has anti-tumor properties, and they started to use the BCG in humans. They found that it can be used in lymphoma and melanoma in the 1970s.

One thing I want to mention here in case you are not involved in research, is that the cancer biology between bladder cancer and melanoma are very similar, especially when they are very responsive to immunotherapy. So now there are many researches to translate the treatment of melanoma to bladder cancer as well.

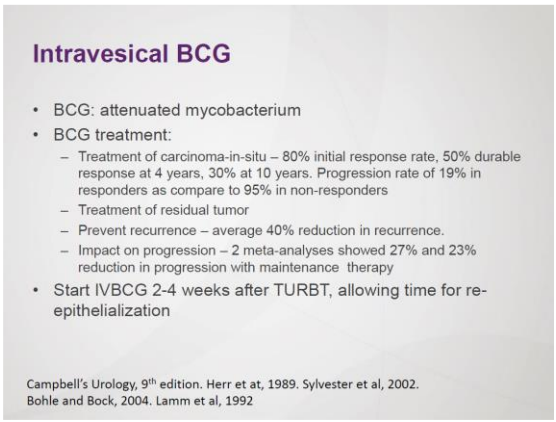
Afterwards, deKernion reported treating bladder melanoma by BCG in 1975. Take note that the very first



Slide 5



Slide 6



Slide 7

case to claim using BCG had bladder melanoma instead of real urothelial bladder cancer. This is very odd, but history is history. They treated the bladder melanoma and found some success.

Morales, a famous urologist in Canada, published the first use of topical BCG on bladder cancer in 1976 [Slide5], just around when I was born. Six weeks treatment was given (Why six weeks? Nobody knows, but it is likely that they used this as the standard as the package consisted of six separate vials.) and more than three weeks of treatment was mandatory to establish a delayed hypersensitive reaction. This is also the reason why at present we give three weekly doses in each maintenance therapy because it can maintain the hypersensitive reactions. In his study of ten patients, intravesical BCG reduced recurrence and eradicated tumor in seven patients, so it all started from there. [Slide 5]

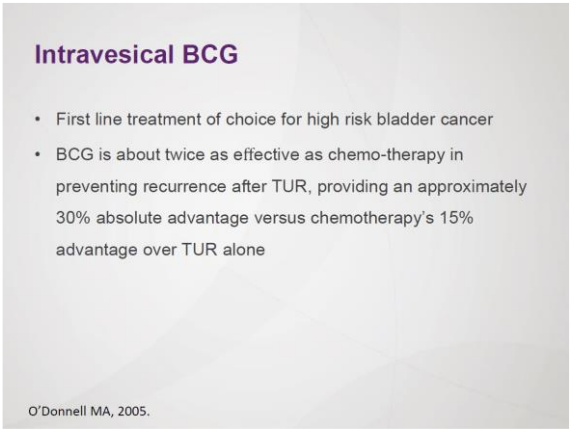
Then, based on these encouraging results, Morales and Lamm started a randomized control trial, and interestingly, they found that BCG really works [Slide 6]. And until now, we are still using BCG as one of the best drugs to use in bladder cancer treatment. It is one of the mainstay treatments for bladder cancer.

As I have highlighted here [Slide 6], BCG has so far been confirmed to reduced recurrence especially in higher risk non-muscle-invasive bladder cancer; delay progression—I use a question mark because now more people query whether it can delay the progression or not ; eradicate CIS—almost 50% of patients will be treated by BCG if they have a carcinoma in situ (CIS) and up to 75% of CIS can be treated by using the second course; and BCG *may* improve survival—also a question mark. That meaning that higher risk bladder cancer patients are better to receive BCG than intravesical chemotherapy.

So, BCG in summary is an attenuated mycobacterium. I think the evidence is already stated in my slides but in short it is a treatment of CIS—80% initial responses, and 50% durable response in four years; it can eradicate some of the residual disease after the transurethral resection of bladder cancer; it prevents recurrence; and *may* impact progression. [Slide 7]

There are two meta-analyses talking about 25% reduction in progression but frankly speaking, a lot of people, especially Henry Herr doubt this data because the

dataset is rather dominated by one major center having a lot of patients with positive outcomes, resulting in the whole group having a positive outcome. Recently more studies are looking for whether BCG really can prevent progression, and even the AUA has revised their tone regarding reduction of progression as well.

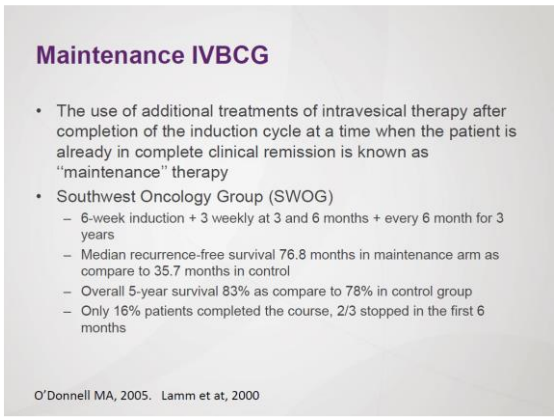


Slide 8

Intravesical BCG is started two to four weeks *after* the TURBT. It is very very important not to give BCG right after TURBT.

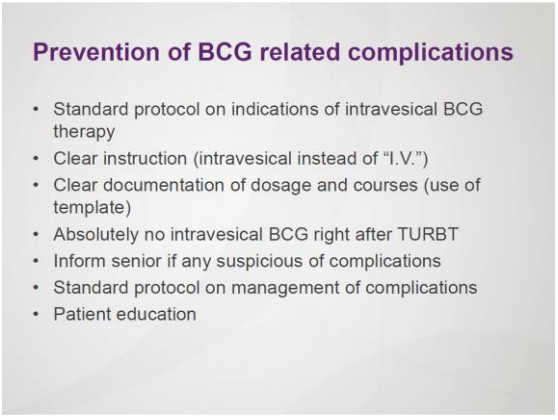
It is the first line treatment for the high risk non-muscle invasive bladder cancer and is twice as effective as chemotherapy. [Slide 8]

Finally, one word on maintenance [Slide 9]. Maintenance is used in Macau and Japan but now some centers, especially Henry Herr may not give maintenance anymore and there are people who question the use of maintenance.



Slide 9

(Discussion)
Dr. Chan : In Macau, how long do you use maintenance?
Floor : Three years
Dr. Chan : So just like the Lamm study. How about in your center in Japan?
Dr. Kikuchi: Three years, but depending on the patient's frequency.
Dr. Chan : Right now in Hong Kong we use just one year, because studies show that one to three years are similar but the tolerance may be difficult for most patients. But we still do not know the optimal duration of the maintenance therapy.

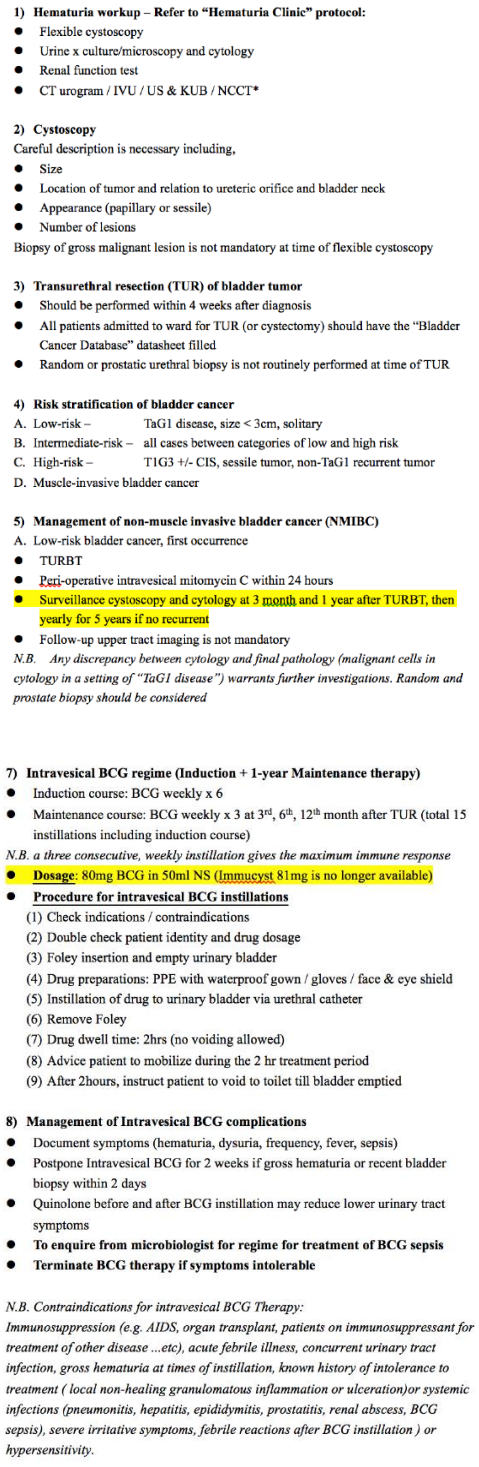


Slide 10

So how about the complications of intravesical BCG therapy? You may expect me to talk about how to treat these, but to avoid overlap, I will focus on **Prevention: How we really practically see a patient when they are going to have BCG therapy.** We will definitely receive calls from our house officers or even our patients, but what can we do before they really complain?

Prevention of BCG-related Complications

I would say that prevention of BCG-related complications is very important. It is not well-documented or well-read in the literature, so I will explain one point after another. [Slide 10]



1) Hematuria workup – Refer to "Hematuria Clinic" protocol:
- Flexible cystoscopy
- Urine x culture/microscopy and cytology
- Renal function test
- CT urogram / IVU / US & KUB / NCCT*

2) Cystoscopy
Careful description is necessary including,
- Size
- Location of tumor and relation to ureteric orifice and bladder neck
- Appearance (papillary or sessile)
- Number of lesions

Biopsy of gross malignant lesion is not mandatory at time of flexible cystoscopy

3) Transurethral resection (TUR) of bladder tumor
- Should be performed within 4 weeks after diagnosis
- All patients admitted to ward for TUR (or cystectomy) should have the "Bladder Cancer Database" datasheet filled
- Random or prostatic urethral biopsy is not routinely performed at time of TUR

4) Risk stratification of bladder cancer
A. Low-risk – TaG1 disease, size < 3cm, solitary
B. Intermediate-risk – all cases between categories of low and high risk
C. High-risk – T1G3 +/- CIS, sessile tumor, non-TaG1 recurrent tumor
D. Muscle-invasive bladder cancer

5) Management of non-muscle invasive bladder cancer (NMIBC)
A. Low-risk bladder cancer, first occurrence
- TURBT
- Peri-operative intravesical mitomycin C within 24 hours
- Surveillance cystoscopy and cytology at 3 month and 1 year after TURBT, then yearly for 5 years if no recurrent
- Follow-up upper tract imaging is not mandatory

N.B. Any discrepancy between cytology and final pathology (malignant cells in cytology in a setting of "TaG1 disease") warrants further investigations. Random and prostate biopsy should be considered

7) Intravesical BCG regime (Induction + 1-year Maintenance therapy)
- Induction course: BCG weekly x 6
- Maintenance course: BCG weekly x 3 at 3rd, 6th, 12th month after TUR (total 15 instillations including induction course)

N.B. a three consecutive, weekly instillation gives the maximum immune response
- **Dosage**: 80mg BCG in 50ml NS (Immucyst 81mg is no longer available)
- **Procedure for intravesical BCG instillations**
  (1) Check indications / contraindications
  (2) Double check patient identity and drug dosage
  (3) Foley insertion and empty urinary bladder
  (4) Drug preparations: PPE with waterproof gown / gloves / face & eye shield
  (5) Instillation of drug to urinary bladder via urethral catheter
  (6) Remove Foley
  (7) Drug dwell time: 2hrs (no voiding allowed)
  (8) Advice patient to mobilize during the 2 hr treatment period
  (9) After 2hours, instruct patient to void to toilet till bladder emptied

8) Management of Intravesical BCG complications
- Document symptoms (hematuria, dysuria, frequency, fever, sepsis)
- Postpone Intravesical BCG for 2 weeks if gross hematuria or recent bladder biopsy within 2 days
- Quinolone before and after BCG instillation may reduce lower urinary tract symptoms
- **To enquire from microbiologist for regime for treatment of BCG sepsis**
- **Terminate BCG therapy if symptoms intolerable**

N.B. Contraindications for intravesical BCG Therapy:
Immunosuppression (e.g. AIDS, organ transplant, patients on immunosuppressant for treatment of other disease ...etc), acute febrile illness, concurrent urinary tract infection, gross hematuria at times of instillation, known history of intolerance to treatment (local non-healing granulomatous inflammation or ulceration)or systemic infections (pneumonitis, hepatitis, epididymitis, prostatitis, renal abscess, BCG sepsis), severe irritative symptoms, febrile reactions after BCG instillation) or hypersensitivity.

Figure 11. Treatment Protocol (extracts)

1. Standard Protocol on indications of intravesical BCG

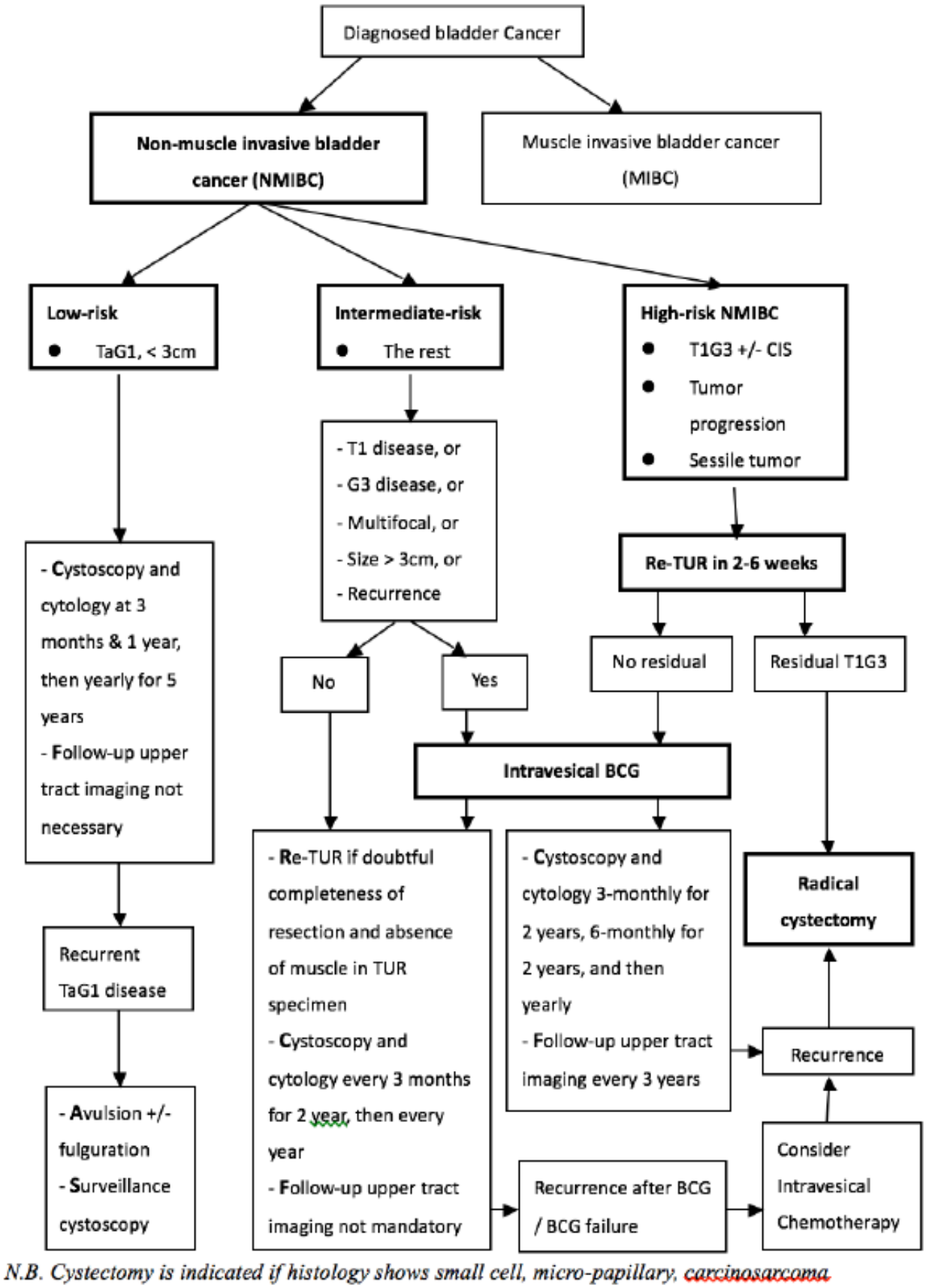
The first is to have a standard protocol on the indications of intravesical BCG. Why is this important? It is because we don't want to over-use or under-utilize BCG.

In my hospital or cluster we have many doctors, and *when* they will offer BCG is very important. On the one hand if patients don't need any treatment but are given BCG, the complications may be not worth it at all. On the other hand if they have high-risk non-muscle-invasive bladder cancer, even if they have some complications or discomfort is could possibly be worthwhile to do so, although of course we try to minimize the unnecessary complications.

Figure 11 is an extract from our protocol on bladder cancer treatment. This is constructed by myself for six to eight years—of course with revisions. But the important part is the flow chart [Figure 12]. When will our patients really need BCG? This YES and NO flowchart first differentiates between high-risk, intermediate- and low-risk, and if they are high-risk, then it decides whether they will have BCG or not, or whether they will have a second TURBT. This flow chart makes sure that neither myself nor a senior need to see every single patient as everyone will follow the protocol.

Also having clear documentation for *how* to give BCG is important because our doctors and nurses should know how long and how to give BCG. Even when it comes to the management of intravesical BCG complications, we have a flow chart on to how to deal with these.

Flow Chart 2 – Management of non-muscle invasive bladder cancer



N.B. Cystectomy is indicated if histology shows small cell, micro-papillary, carcinosarcoma

Figure 12. Flow Chart

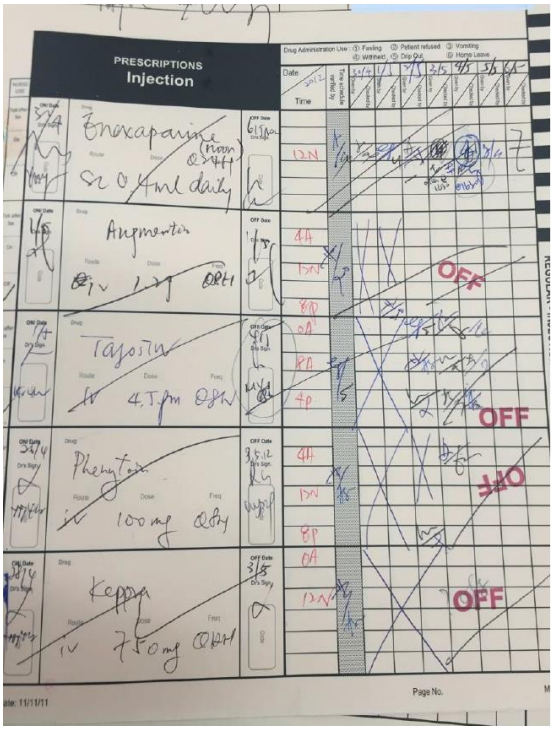


Figure 13. Drug Chart

Schedule of Flexible Cystoscopy and IVBCG for Patients with Bladder Cancer[1]
(Please put this in the first part of the notes after The first dose of IVBCG)

GUM LABEL

TURBT Date _____ Pathology T: G:

Induction: Started at least 3 weeks after TUR

	Date	Done?	Remarks
Weekly Induction 1		☐	
Weekly Induction 2		☐	
Weekly Induction 3		☐	
Weekly Induction 4		☐	
Weekly Induction 5		☐	
Weekly Induction 6		☐	
3rd – Month FC		☐	
+ IVBCG (same day)		☐	
2nd week IVBCG		☐	
3rd week IVBCG		☐	
6th – Month FC		☐	
+ IVBCG (same day)		☐	
2nd week IVBCG		☐	
3rd week IVBCG		☐	
9th – Month FC			
12th – Month FC		☐	
+ IVBCG (same day)		☐	
2nd week IVBCG		☐	
3rd week IVBCG		☐	

Then continue surveillance cystoscopy according to guideline
Return this form to Ms. Cleo Lam at time of last IVBCG instillation

Figure 14. Proforma

2. Clear instruction (intravesical not "I.V." BCG)

At the second is clear instruction.
When we see a patient and we know that they need BCG, we explain and obtain their consent, and arrange BCG treatment.

Here is one of our typical drug charts [Slide 13]. I'm not sure if it is similar in Macau, and of course this is not a drug chart for BCG, but can you see that we may write "I.V."? And actually in the past we would call intravesical BCG "I.V. BCG", but as you know BCG cannot be given intravenously!

You may say that this is a stupid mistake and no-one will really inject BCG intravenously, but I am sorry to say, even chemotherapy has been given through a different route in different ways. It happens. It happens especially when your hospital does not use BCG very often, and your nurses have not given BCG on many occasions at all.

So, right now in my hospital and all public hospitals in Hong Kong, we will write "Intravesical BCG" in full, and even better now, we use a computer and check the box for "Intravesical BCG". I am not sure if it is similar in Macau or elsewhere, but if it is also like this, do take care. A mistake is a mistake and it is stupid, and it may happen to you and you will regret it.

3. Clear documentation on dosage and courses (use of template)

The third is clear documentation on dosage and course, as well as the use of a template.

Here is the proforma of a patient. For every patient that we arrange BCG, they will have a proforma in their notes just like this [Slide 14].

First of all, you will see *when* they had TURBT. Importantly, it should not be within two weeks from TURBT. Also you check the pathology. If you find something suspicious, for example if you see 'T2', then you should question about it.

Then comes weekly inductions 1-6 with the dates that you have fixed for the patient. So they follow according to this schedule and once this is done, if anything happens, you write in the remarks.

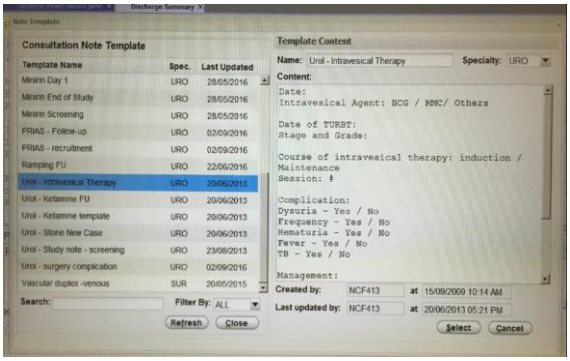


Figure 15. Electronic template

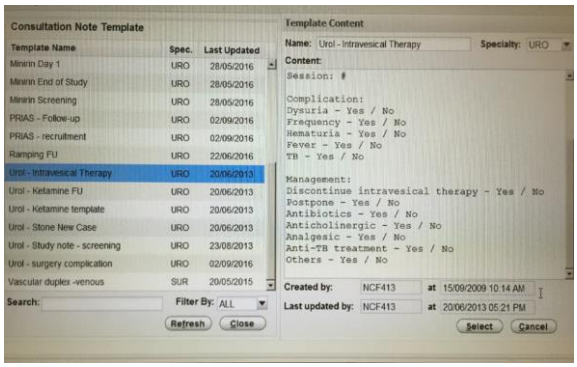


Figure 16. Electronic template

Figure 17. Surgical ward (left) and Surgical ambulatory care center (right)

Then for 3 months cystoscopy, 6 months, 9 months, and 12 months you will also have the date for them. And if in the third month of cystoscopy there is no recurrence, they can proceed for an intravesical BCG on the same day and continue for the third month, same for the sixth month. Right now we omit the ninth month and give the 12th month.

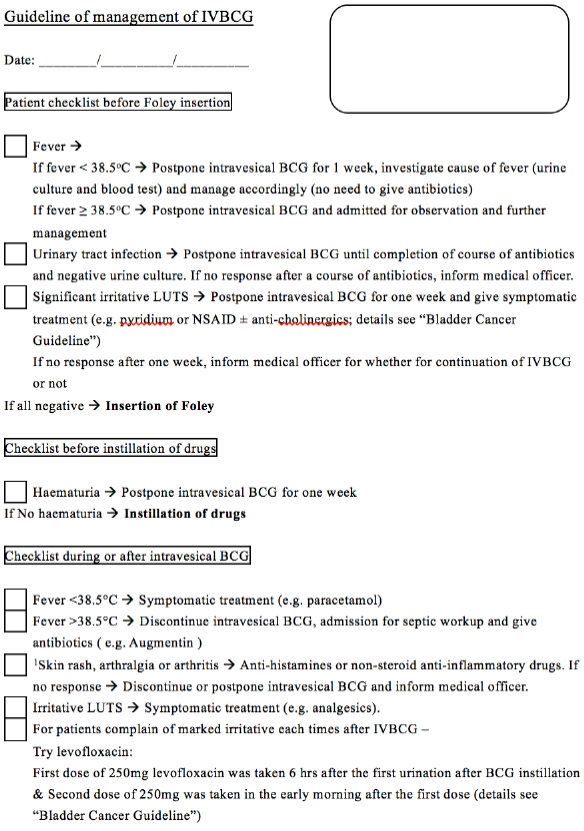
So, all of our patients who have BCG treatment will have a proforma in their notes with clearly stated dates and remarks. Even when they go home, they we will also have a discharge summary. We have a template which will include the date, what agent they are given, date of TURBT and stage, the course, whether in this admission/treatment it is an induction or maintenance, and what session number it is [Figure 15].

Initially this template was used for my research, but actually it is also very handy for the patient. It is very simple. The next time the house officers or doctors want to check the causes, they can go back to the computer notes as well as the proforma. They will know whether there were complications (Yes/No) in the last time. They will also know about any management, including whether BCG was discontinued, postponed, antibiotics, analgesics, anticholinergic, or even anti-TB treatments were given etc. [Figure16]. So everything is stated very clearly in this simple template.

4. Absolutely no intravesical BCG right after TURBT.

Absolutely no intravesical BCG right after TURBT. You may say again that it is very stupid and everybody knows, but I have to say NO, a lot of people may not know about this.

In my hospital there are two groups of patients [Figure 17]. On the left side is the ward where we admit the patients after TURBT and discharge here, and all the other patients who receive intravesical BCG will be in our day center on the right. So this means that in the surgical ward they will never prescribe BCG and that they will never mistakenly use it on patients right after TURBT. All the BCG instillation will only be the day center. So easy, no doubt about it, right?



Guideline of management of IVBCG

Date: _____/_____/_____

Patient checklist before Foley insertion

☐ Fever →
If fever < 38.5°C → Postpone intravesical BCG for 1 week, investigate cause of fever (urine culture and blood test) and manage accordingly (no need to give antibiotics)
If fever ≥ 38.5°C → Postpone intravesical BCG and admitted for observation and further management

☐ Urinary tract infection → Postpone intravesical BCG until completion of course of antibiotics and negative urine culture. If no response after a course of antibiotics, inform medical officer.

☐ Significant irritative LUTS → Postpone intravesical BCG for one week and give symptomatic treatment (e.g. pyridium or NSAID ± anti-cholinergics; details see "Bladder Cancer Guideline")
If no response after one week, inform medical officer for whether for continuation of IVBCG or not

If all negative → **Insertion of Foley**

Checklist before instillation of drugs

☐ Haematuria → Postpone intravesical BCG for one week

If No haematuria → **Instillation of drugs**

Checklist during or after intravesical BCG

☐ Fever <38.5°C → Symptomatic treatment (e.g. paracetamol)
☐ Fever >38.5°C → Discontinue intravesical BCG, admission for septic workup and give antibiotics (e.g. Augmentin)

☐ [1]Skin rash, arthralgia or arthritis → Anti-histamines or non-steroid anti-inflammatory drugs. If no response → Discontinue or postpone intravesical BCG and inform medical officer.

☐ Irritative LUTS → Symptomatic treatment (e.g. analgesics).

☐ For patients complain of marked irritative each times after IVBCG –
Try levofloxacin:
First dose of 250mg levofloxacin was taken 6 hrs after the first urination after BCG instillation & Second dose of 250mg was taken in the early morning after the first dose (details see "Bladder Cancer Guideline")

Figure 18. Guideline of management of IVBCG

Figure 19. Patient booklet

5. Standard protocol on the management of complications of BCG &,
6. Inform senior if any suspicions on complications

The next point is the standard protocol on the management of complications of BCG. I've already talked a little about this but these are the guidelines for the management of BCG [Figure 18].

Sometimes we will check according to the checklist: Does the patient have hematuria? If yes, what can we do? If it's very light they will ask a senior to have a look, and if it is severe, they need to stop or withhold or abandon or postpone the treatment. If they have hematuria or if they have a fever or previous urinary tract infections, or significant irritative symptoms… All this will be right before you really give the drugs or BCG.

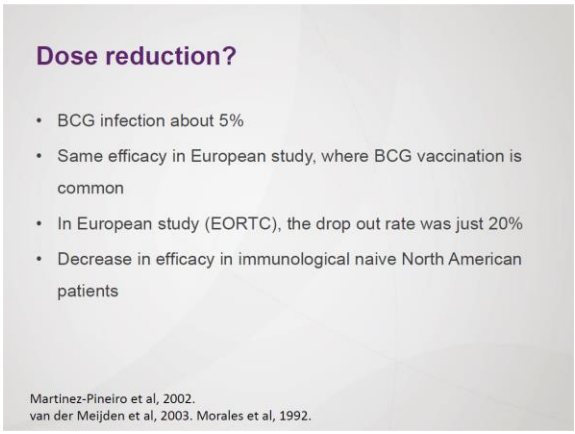
And how about after you give the intravesical BCG? Do they have a fever of less than 38.5℃? If yes but less than 38.5℃, give them some rest or antibiotics. If the fever is higher, then you may need to admit the patient and do sepsis workup. Sometimes if irritative symptoms appear, you can give them analgesics.

So all these things are very clear with the checklist in the day ward. The nurse will put it on the patient's folder and in my hospital, the drugs will be given by the house officers or the interns so obviously they won't stay long, but with this check-list they will know what to do, and I won't need to go to the day ward to check on every single patient.

7. Patient education

Lastly I will speak about patient education.
You received a booklet [Figure 19] when you came in and actually this is very well written. So whenever a patient needs to call the doctor or go to the A&E, it can save you a lot of time and trouble, because the patient will go to seek help earlier if they have a problem, and more importantly, if it is a minor issue, they will not call you up if it is something they can treat at home by themselves.

Patients need to know what to do if they find some problems, and the advantage is that once they have the information, they will voluntarily talk to the doctor next time if they find any problems in the last BCG instillation.



Slide 20

Dose Reduction

This is most of my talk for today, but before I hand over to Doctor Kikuchi, I'd like to mention that dose reduction is also one option. When I find complications in my patients, I may try to give a dose reduction. Even for older patients of 80-something that are deemed to need BCG, I will try to use a dose reduction.

One more interesting thing is that in the past all our studies used a 1/3 dose. Do you know the reason? In the past BCG came in three vials. 81mg= 27mg x 3 vials. You could not reduce in half. So we used one vial. So this is some of the history.

Finally some announcements:

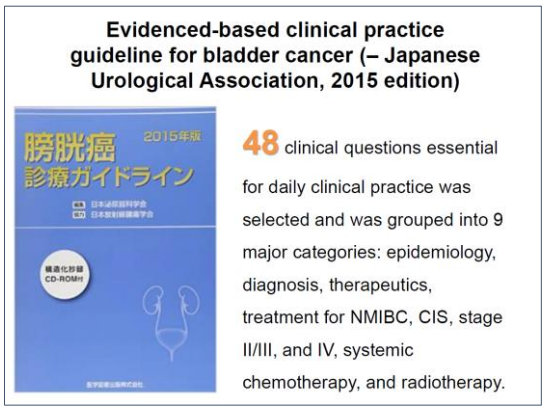
In November we have the urology symposium in Chinese University of Hong Kong in my center on the 4th and 5th, and hopefully we will see you come and join us and we will have more discussions. This year is very interesting —we are taking a multi-disciplinary approach on care in urology. It means that we are not just urologists but we work closely with others: not just oncologists, but physiotherapists, dieticians, ENT surgeons… Why? Come and you will know.

Lastly the UAA 2017 will take place in August in Hong Kong. Hopefully Dr. Kikuchi would also join us so we are looking forward to that.

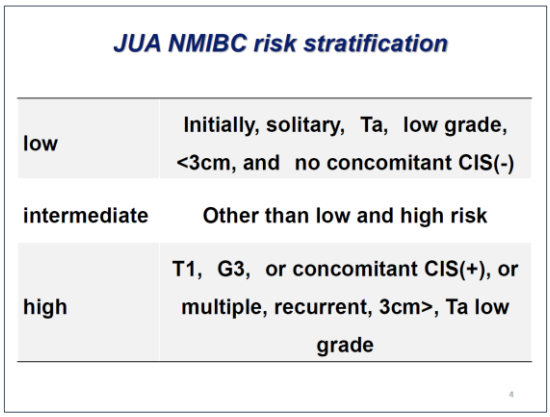
Thank you very much.

Dr. Eiji Kikuchi

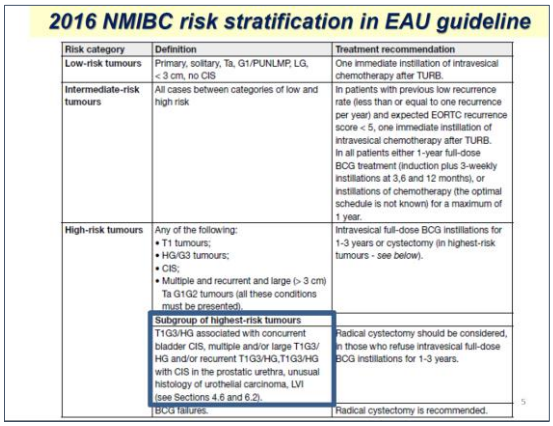
Clinical Questions for BCG Therapy in Non-Muscle-Invasive Bladder Cancer



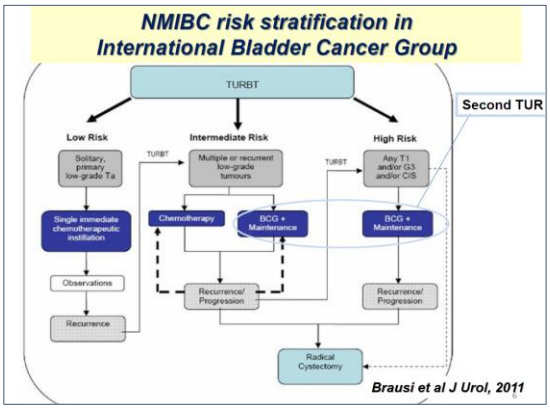
Slide 1



Slide 2



Slide 3



Slide 4

Today I have prepared four clinical questions in regard to BCG therapy against non-muscle-invasive bladder cancer (NMIBC) in Japan.

CQ I. Who should be treated with BCG therapy for NMIBC?

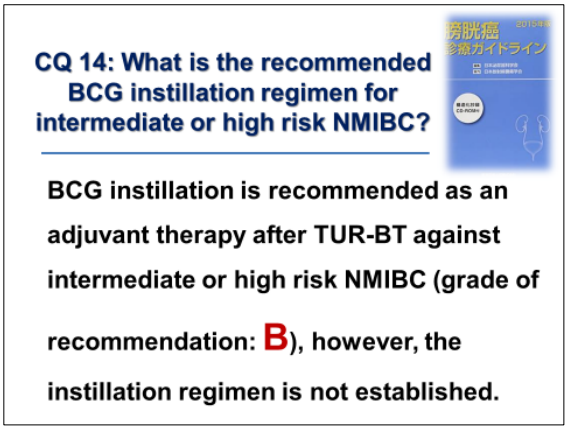
Some Japanese urologists worry about who should be treated by BCG, and who can be treated by intravesical chemotherapy. To discuss the question, I need to refer to the NMIBC risk stratification, because treatment decisions of BCG therapy is determined accordingly.

First of all, I would like to introduce our new revised clinical guideline for NMIBC in Japan. The Japanese Urological Association (JUA) revised their evidence-based clinical guideline for NMIBC in April 2015, and there are 48 clinical questions essential for daily clinical practice for NMIBC and nine major categories: epidemiology, diagnosis, therapeutics, treatment for NMIBC, CIS, stage II/III, and IV, systemic chemotherapy, and radiotherapy. [Slide 1]
According to the JUA guideline, NMIBC can be stratified into three risk groups as shown here [Slide 2].

The stratification in the EAU guideline for NMIBC is almost the same as JUA's. There are three risk stratifications, however high-risk tumors are sub-divided into two groups and include a subgroup of 'highest-risk' tumors. 'Highest risk' tumors are as shown in Slide 3.

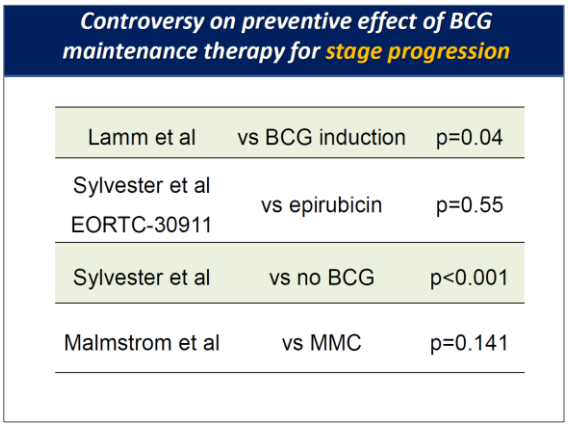
Furthermore, experts for NMIBC in International Bladder Cancer Group (IBCG) have established a risk classification for NMIBC [Slide 4] . 'Low risk' was defined as solitary, primary, low-grade Ta tumor, and 'Intermediate risk' was defined as multiple or recurrent low-grade tumors, and 'High risk' was defined as any T1, and/or G3, and/or CIS tumor. I think it is very simple and easy to use in clinical practice and this is the stratification I use today.

According to the IBCG risk stratification, some of the intermediate risk tumors and most of the high risk tumors need to be treated with BCG either by induction or maintenance therapy.

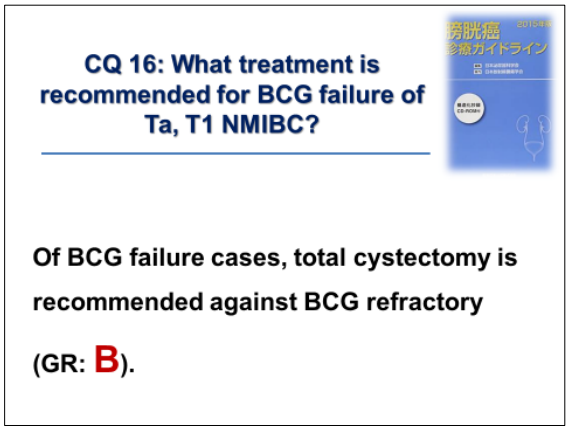


Slide 5

Slide 6



Slide 7



Slide 8

So the answer for the first question is that BCG induction or maintenance therapy is needed for some of the intermediate risk group and most of the high risk group.

Here, I would like to briefly introduce the JUA Guideline's seven clinical questions in regard to BCG therapy.

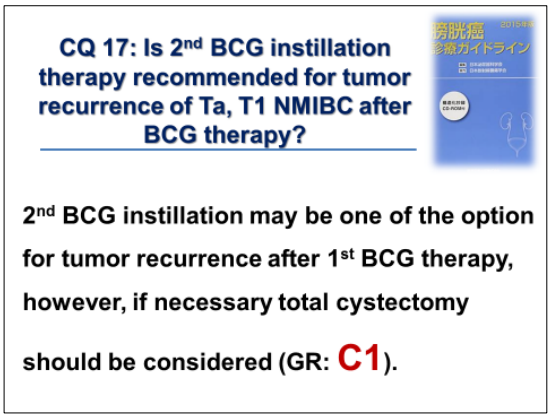
First, *CQ14: **What is the recommended BCG instillation regimen for intermediate or high risk NMIBC?*** ［Slide 5］
Of course, BCG therapy is very effective for prevention of tumor recurrence and therefore it is recommended as an adjuvant therapy after TURBT against intermediate or high risk NMIBC (grade of recommendation: B). However we have not yet established the exact regimen. Is it six times or eight times? Maintenance or not? We do not yet know.

Second, *CQ15: **Is BCG maintenance therapy recommended for intermediate or high risk NMIBC?***
［Slide 6］
Yes, maintenance therapy is recommended in Japan (GR: B) but only roughly 20-30% of patients with high risk tumor is actually treated with maintenance therapy. We usually do induction therapy. But in my opinion, highest risk tumors need to be treated with maintenance therapy.

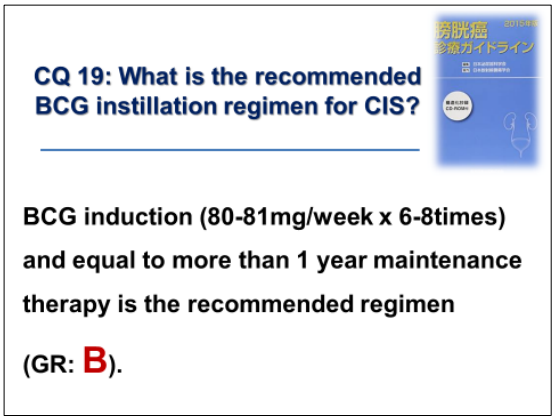
Dr. Eddie already mentioned about the stage progression, and the JUA guideline also mentions about the effect of BCG maintenance therapy for reducing stage progression, but this is controversial. Two RCTs and two meta-analyses are shown here［Slide 7］.

The RCT reported by Lamm et al. demonstrated the superiority of maintenance therapy in comparison to BCG induction therapy for the prevention of stage progression. However, Sylvester et al. demonstrated no difference between BCG and epirubicin therapy in their RCT study. Interestingly however, Sylvester mentions the superiority of maintenance therapy over induction therapy in a meta-analysis as shown here. Malmstrom et al. meanwhile reported no difference with mitomycin C instillation in their meta-analysis.

This is why the JUA still cannot take a stance regarding the prevention of stage progression by BCG. This controversy should be resolved in the future.

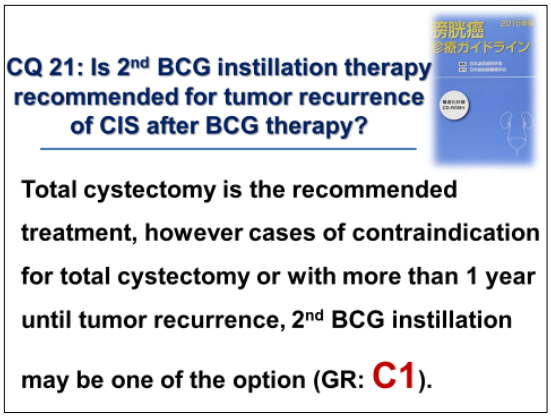


Slide 9



Slide 10

Slide 11



Slide 12

Next, *CQ16: What treatment is recommended for BCG failure of Ta, T1 NMIBC?* ［Slide 8］
BCG refractory which cannot be cleared within six months of BCG therapy need to be treated with total cystectomy (GR: B).

CQ17: Is a 2nd BCG instillation therapy recommended for tumor recurrence of Ta, T1 NMIBC after BCG therapy? ［Slide 9］
A second BCG instillation may be one of the options for tumor recurrence after the first BCG therapy, however if necessary total cystectomy should be considered (GR: C1). But I must add that most of the patients in Japan don't want to receive total cystectomy, so most patients will be treated with BCG therapy, especially maintenance therapy.

CQ19: What is the recommended BCG instillation regimen for CIS? ［Slide 10］
The recommendation is BCG induction (80-81mg/week × 6-8 times). Usually we treat first CIS by induction therapy, however equal to more than one year of maintenance therapy is the recommended regimen (GR: B) for BCG failure patients with CIS.

CQ20: Is BCG maintenance therapy recommended for CIS? ［Slide 11］
BCG maintenance therapy is recommended for CIS (GR: A).

CQ21: Is a 2nd BCG instillation therapy recommended for tumor recurrence of CIS after BCG therapy? ［Slide 12］
Total cystectomy is the recommended treatment, however in cases of contraindication for total cystectomy or in cases of one or more than one year until tumor recurrence, 2nd BCG instillation may be one of the options (GR: C1).

Purpose

To examine the rate of side effects of BCG and to investigate whether occurrence of BCG side effects could affect tumor recurrence in NMIBC patients treated with induction course of BCG.

Patients

- 145 NMIBC patients
- 1996-2006
- At our institution

Takeda T, Kikuchi E et al, Urology, 2009

Slide 13

Side effects

	case	%
Bladder contracture	1	0.7%
Epididymitis	1	0.7%
Hematuria persisting for ≥2 days	7	4.8%
Hematuria within 2 days	50	34.5%
LUTS persisting for ≥2 days	13	9%
LUTS within 2 days	60	41.4%
Fever persisting for ≥2 days	20	13.8%
Fever within 2 days	20	13.8%
Overall	106	73.1%

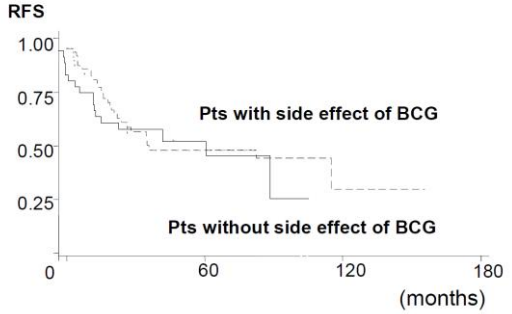
Slide 14

Predictors for tumor recurrence

	Uni-	Multi-
	p value	p value
Age	0.212	
Sex	0.706	
Multiplicity	0.036	0.038
Tumor grade	0.945	
Tumor stage	0.260	
Concomitant CIS	0.250	
Occurrence of side effect	0.935	
Discontinuance of BCG	0.021	0.025

Slide 15

K-M curve between pts with side effect and those without



Slide 16

CQII: Could patients with side effects have a better therapeutic response to BCG therapy?

I move on to the next clinical question. Some researchers have suggested a possible association between the local and systemic side effects of BCG instillation and its efficacy.

So here is the clinical question: Could patients with side effects have a better therapeutic response to BCG therapy? Many Japanese doctors think that if the patient has severe side effects, then BCG can treat everything. Is this correct?

Previously we examined the rate of side effects of BCG and investigated whether occurrence of BCG side effects could affect tumor recurrence in NMIBC patients treated with an induction course of BCG［Slide 13］. We identified 145 NMIBC patients from 1996 to 2006 in our institution and published this data in Urology in 2009.

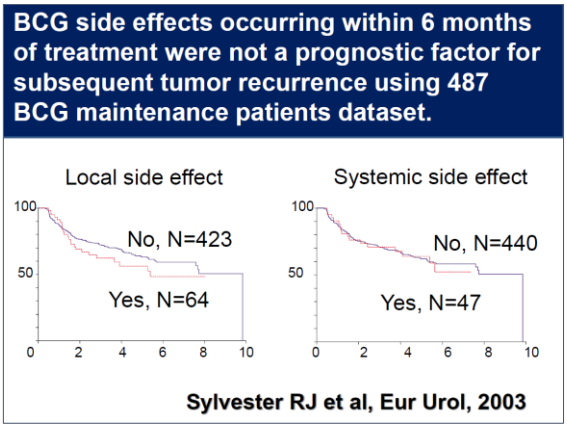
These patients were treated with the Tokyo strain. BCG was scheduled for weekly administration for six weeks for stage Ta-T1 tumors and for eight weeks for CIS at a dose of 80mg of BCG in 40 mL of saline for one to two hours. I think Dr. Eddie said he uses 50mL in his department, but we use 40mL of saline for one to two hours.

The side effects profiles are listed here ［Slide 14］. Bladder contracture, or epididymitis occurred in only 1 cases each. Hematuria persisting for equal or more than two days was seen in 4.8%. Lower urinary tract symptoms persisting for equal or more than two days were seen in 9%. Fever persisting for equal or more than two days was seen in 13.8%.

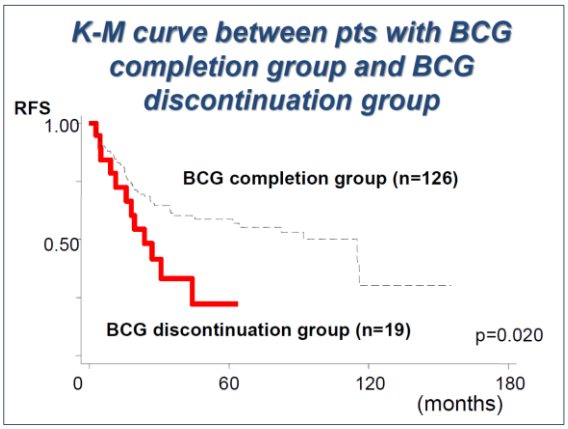
Multivariate analysis demonstrated that occurrence of side effects was not a significant predictor for tumor recurrence. On the other hand, discontinuance of BCG therapy was independently associated with tumor recurrence［Slide 15］.

A Kaplan-Meier curve demonstrated that no significant difference on recurrence-free survival was observed between patients with side effects of BCG and those without［Slide 16］.

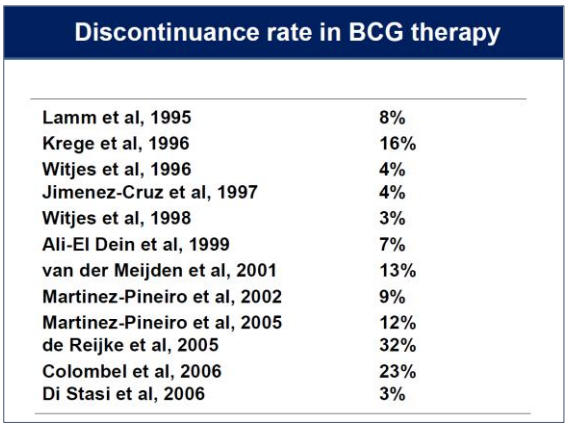
Also Sylvester et al. reported that BCG side effects occurring within six months of treatment were not a



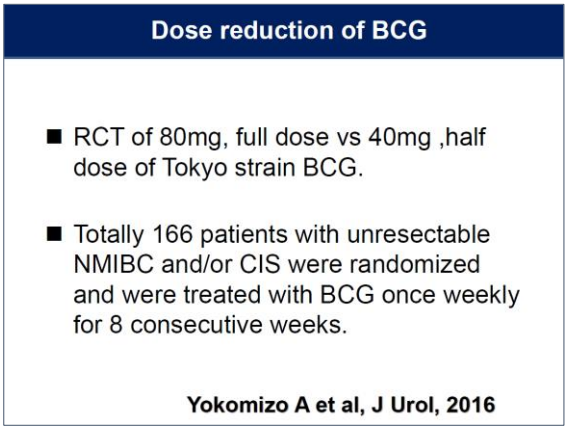
Slide 17



Slide 18



Slide 19



Slide 20

prognostic factor for subsequent tumor recurrence, using 487 BCG maintenance patients' dataset on local and systemic side effects, so our result is similar to theirs［Slide 17］.

As I said, patients in BCG discontinuation group had worse recurrence-free survival compared to patients in BCG completion group. So I would like to say that: to complete the BCG therapy is very important for preventing tumor recurrence［Slide 18］.

Slide 19 is a list which shows the discontinuance rate of BCG therapy from previous published literatures and it ranged from 3% to 32%.

So the message from my second clinical question is that:

- Occurrence of major side effects of BCG therapy is 5-14%. There is no association between occurrence of BCG side effects and tumor recurrence.
- BCG discontinuance cases (also called intolerance cases) are 3-32%
- Discontinuance of BCG therapy for NMIBC might have a negative effect on tumor recurrence, so we need to complete the BCG regimen.

So in order to complete the regimen;

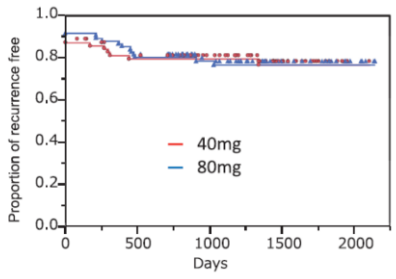
CQ III. How do we reduce BCG side effects?

Dr. Eddie has already talked a little about this so I will skip some parts, but dose reduction of BCG might be one of the useful management for reducing the side effects in NMIBC patients using BCG.

Quite recently, Yokomizo et al. have reported the results of an RCT of 80mg (=full dose) vs 40mg (=half dose) of Tokyo strain BCG. Totally 166 patients with unresectable NMIBC and/or CIS –so all these tumors are the 'highest risk' group—were randomized and treated with BCG once weekly for eight (not six) consecutive weeks［Slide 20］. No difference in CR rate, RFS, PFS, and OS between the two groups were observed［Slide 21］. On the other hand, side effects profile was significantly different. The incidence of fever in patients treated with a half-dose was 9% while 28% in full-dose patients, and micturition pain was observed in 68% for half-dose group and 87% for full dose［Slide 22］.

So if I see a patient who has a severe side effect then we

■ No difference in CR rate, RFS, PFS, and OS between the two groups.



Yokomizo A et al, J Urol, 2016

Slide 21

■ Grade 2 or more rate CTCAE 3.0 between the two groups.

	40mg	80mg	P value
Fever	9%	28%	0.001
Fatigue	26%	27%	0.837
Micturition pain	68%	87%	0.047
Urgency	80%	78%	0.459

Yokomizo A et al, J Urol, 2016

Slide 22

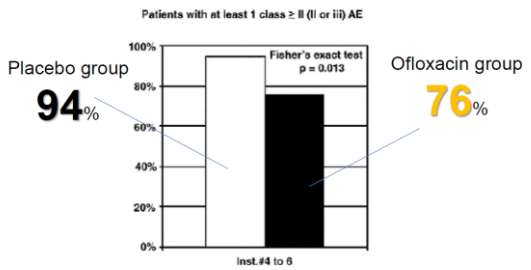
Prophylactic use of fluoroquinolone

■ RCT of BCG plus 200mg ofloxacin, vs BCG plus placebo.

■ Totally 115 patients with primary or recurrent Ta/1, CIS, G1-3 were randomized.

Marc C et al, J Urol, 2006

Slide 23



■ Prophylactic ofloxacin decreased the incidence of moderate to severe adverse events associated with BCG.

Marc C et al, J Urol, 2006

Slide 24

change from 80mg to 40mg. In this way, they can be treated continuously.

Also, prophylactic use of a fluoroquinolone which has sensitivity to BCG, might also be one of the useful management methods for reducing the side effects of BCG.

Marc et al. have reported the outcome of RCT of BCG plus 200mg ofloxacin, vs BCG with placebo［Slide 23］. Totally 115 patients were treated with this regimen, and they found a significant difference in the incidence of BCG side effects between the two groups［Slide 24］. The ofloxacin group had a better side effect profile so they concluded that prophylactic ofloxacin decreased the incidence of moderate to severe adverse events associated with BCG.

The International Bladder Cancer group (IBCG) proposed the following instructive recommendations for prevention of BCG-associated adverse events. I usually recommend these to my residents to learn how to do BCG therapy.

- Instill BCG after a minimum of two weeks following a TURBT (But I usually wait one month because I usually treat the patients by second deep TUR)
- Teach proper catheterization techniques to administering health care professionals.
- Defer BCG instillations for one week if catheterization is traumatic.
- If gross hematuria is present, delay BCG until this has resolved.
- If the patient has a UTI, then defer BCG for one week until resolution of the UTI with antibiotics.
- Consider the use of ofloxacin 200 mg given twice after each BCG instillation.
- If a BCG systemic reaction is suspected, then initiate multiple antimicrobial therapies early and consult with an infectious diseases specialist. And,
- Consider dose reductions in patients known to be intolerant to standard-dose BCG.

I think these recommendations are very useful for BCG treatment in daily clinical practice.

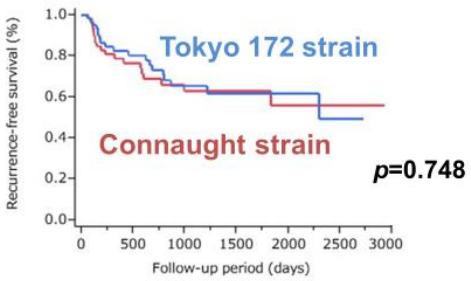
Tokyo 172 strain vs Connaught strain

- RCT of Tokyo 172 strain vs Connaught strain.
- Totally 129 patients were randomized.
- However, the manufacturer of the Connaught strain announced that production would be suspended in June 2012 due to renovations to the manufacturing facility.

Sengiku A et al, J Urol, 2013

Slide 25

Two different strains on RFS



Sengiku A et al, J Urol, 2013

Slide 26

Two different strains on side effects

	Tokyo 172	Connaught
Cystitis	64%	54%
Fever	27%	26%
Macroscopic hematuria	9%	12%
Burning	21%	24%
Frequency at night	17%	13%

Sengiku A et al, J Urol, 2013

Slide 27

I move on to the final clinical question.

CQ IV. Could Tokyo 172 strain have stronger therapeutic effects on NMIBC than Connaught strain?

In Japan, two different preparations have been used in the past: Immunobladder® (BCG Tokyo 172 strain) and ImmuCyst® (Connaught strain). So we have never used TICE or another type of strain in Japan.

In this regard, Sengiku et al. performed a very elegant RCT［Slide 25］. They compared the Tokyo 172 strain directly against the Connaught strain in 129 patients. However, the manufacturer of the Connaught strain announced that production would be suspended from June 2012 due to renovations to the manufacturing facility, so the study was terminated earlier and analyzed. We still cannot use the Connaught strain in Japan.

The results［Slide 26］showed that there is no significant difference in tumor recurrence between the two strains.

Furthermore, there was no significant difference in the incidence of side effects between the two groups［Slide 27］.

The author's message is as follows:
First, since Connaught strain is supplied to many countries worldwide, suspended production may affect a global shortage of BCG, which may be deleterious for patients with NMIBC.
Second, patients could be treated as effectively and safely with the Tokyo strain as with the Connaught strain.

My final conclusion today is that Tokyo 172 BCG strain is safe and effective for the treatment of NMIBC and I hope that more patients can be treated with the Tokyo 172 BCG strain worldwide.

Thank you for your attention.

Chair: I will open up the floor to questions and discussion

Floor: In Macau we have used BCG intravesical treatment for many years. As Dr. Ian said, we have shifted from another strain to the Tokyo strain, and we have found that the side effects is stronger. We have no study support to know why, but we are facing our patients and having no house officer or other doctors' help so they directly seek my response. There are many inquiries.
I think up to now BCG has been quite good for the superficial bladder cancer treatment and BCG is quite effective to reduce the operation rate, but the main concern is how we can decrease the side effects and your sharing has been impressive and some things we can change a little, but during the past years, we have experienced some severe side effects: severe dysuria, fever etc.
We have learned from the book that sometimes we can use isoniazid, but in your presentation nothing has been mentioned about this medication. What is your opinion on this?

Dr. Kikuchi: First of all, I talk with my patients in regard to their urinary status: 'Do you have dysuria or do you have BPH?' If they have severe dysuria or BPH, then we have to modify their schedule of BCG, for example weekly, not bi-weekly, and dose 80mg not 40mg. So we talk with our patients.
I'm sorry I have never experienced severe side effects. Of course, I have one patient who had a bladder contraction and acute epididymitis, but in my experience I haven't worried about severe side effects before the treatment using BCG Tokyo strain.

Floor: I have to disagree with you because many young patients especially, complain quite strongly about bladder contraction and dysuria as well as gross hematuria so when I see your data I think it is not the same as with us. Maybe reducing dosage is an option but instead of this, is there any medication that can help?

Dr. Kikuchi: Prophylactic antibiotics for example ofloxacin is effective. I only use this one.
From the start of BCG therapy, I talk to the patient carefully that if your bladder cancer cannot be treated by BCG, then you lose the bladder. That young patients may say that they will take BCG anyway, but I think this is also why they will not complain.

Dr. Chan: Just one point- dose reduction would be useful, or quinolone prophylactic is also useful, anticholinergic (Vesicare etc.) during the course of the treatment sometimes it helps. But frankly speaking we haven't seen too much of the severe complications that make the patient readmit to the ward. I think anticholinergic is more routinely given but maybe you can do a study on whether prophylactic or anticholinergic is more effective.

Chair: Question for Eddie. Dr. Kikuchi mentioned that BCG is still controversial for bladder cancer progression. So what is your opinion?

Dr. Chan: Also what I said. I think that most people at the moment mainly active on bladder cancer question the prevention of progression by using BCG. Also we have more data that long BCG treatment may delay the definite treatment of cystectomy as well.
So what I mean is right now the approach is that if BCG cannot be tolerated, we try to postpone, and if

they still cannot tolerate, we stop it. And if there is any bad sign of high risk – for example if we find bladder cancer even in the second TURBT – I won't even give BCG at all because we know that almost half of them will get progressions.

Also as Dr. Eiji has mentioned about the JUA guideline, in the case of a histological variant like micropapillary, it is better not to do the BCG either because that group of patients is at high risk of progression with a really bad tumor. We know that micropapillary is a nasty bladder cancer and it is better to do a definite treatment early.

Dr. Kikuchi: I agree with you. So how do you treat patients with bladder urothelial carcinoma with small amounts of squamous cell or adenocarcinoma components? Or pure squamous and adenocarcinoma?

Dr. Chan: Right now we take all the histological variants very cautiously, whether it be sarcomatoid or other. We don't use the term TCC (transitional cell carcinoma) anymore but if it is anything other than a simple urothelial cancer you need to think twice what you need, even if it is chemo or some other definite treatment, because you will see the patient progress right in front of you during the more bladder conserving treatments.

Floor: I had a case using BCG, and within the six months had the fail because we see the recurrence of the tumor. After the second time TURBT, how do you prevent the tumor recurrence: use a Mitomycin C or second BCG?

Dr. Kikuchi: So if within six months you find a tumor recurrence, now we have another option. It is a PD-1 therapy and cannot be used in clinical practice yet, but we tried to do a PD-1 antibody treatment against such BCG failure cases.
But usually most of the Japanese urologists do a total cystectomy but if the patient is reluctant, then we do BCG therapy again.

Dr. Chan: One follow-up question. First of all it is very interesting to know the use of PD-1 on NMIBC. It just reminds me that in the past ten years many people have been talking about other kinds of immunotherapy or chemotherapy but it seems that none of them worked as expected. What do you think? Is PD-1 is the next one or just like BCG, we have nothing else?

Dr. Kikuchi: I completely agree with you. Maybe immunotherapy such as PD-1 may not work very well, so BCG is better than any other method that I have ever experienced.

Chair: So last question for Dr Eiji. You mentioned that the minimal waiting time for TURBT is two weeks. Recently in our department, we perform TURBT with thulium laser. Do you think the timing of starting BCG is different?

Dr. Kikuchi: I'm sorry I've never experienced laser therapy so I don't know, but there shouldn't be a difference.

Dr. Chan I think there is no difference because you still get a deep cut with a laser. In my hospital we do en-bloc resection as well but everything is disruptive and have a raw scar so you need to wait. This is no rush at all.

Dr. Kikuchi: So you need to compare the healing process in the bladder using animal model. Then you can find the difference. If the healing process is

the same then you better wait at least two weeks.

Floor: Because we use the thulium laser for the TURBT we can see the layers very clearly. We can see the submucosa, the mucosa, the superficial muscle. We can do like that.

Chair: Thank you for the excellent symposium. Thank you Eddie, Thank you Eiji.

This pamphlet has been printed with permission from each of the speakers and Co-hosts. We thank all those who took part in this symposium.