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Original – Bladder cancer

Radical cystectomy in patients with non-muscle invasive bladder cancer who fail BCG therapy

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Objective: To assess the characteristics and outcomes of patients with non-muscle invasive bladder cancer (NMIBC) undergoing radical cystectomy (RC) due to BCG failure.

Materials and methods: Ninety-five (11%) of the 864 patients undergoing radical cystectomy (RC) at our center from 1989 to 2002 had received prior treatment with BCG.

Of these, 62 (65.2%) underwent RC due to relapsing, high-risk NMIBC or CIS despite BCG therapy. A stage ≥ pT2 tumor was reported in the cystectomy specimen in 17 (27%) of these patients, who were considered to have been understaged.

RC was performed for clinical progression in 33 patients (34.7%). Their last transurethral resection before RC showed invasive disease.

A retrospective analysis was made of the outcomes of patients who underwent RC for BCG failure and the clinical and pathological differences between understaged patients and those with clinical progression.

Results: Five-year CSS was 90% in 45 patients with clinical and pathological NMIBC and 50.6% in 50 patients with progression to muscle-infiltrating disease (clinical progresion and understaged) ($p < 0,05$). There were no differences in survival in patients with clinical progresion as compared to understaged patients.

Median time from tumor diagnosis to tumor progresion was 24 months (10th-90th percentile, 6-98 months). Patients with clinical progresion had significantly more T1 tumors ($p = 0.015$) in TUR before progression and more pT3 tumors ($p < 0.01$) in the RC specimen. Understaged patients more often had pathological pT4 stages ($p < 0.02$).

Conclusion: In patients with high-risk NMIBCs who fail BCG therapy, RC should be performed before progression because survival is decreased when the RC specimen shows muscle-invasive disease. High-grade T1 tumors are responsible for most early clinical progressions. Patients with NMIBC may have subclinical progression, mainly within the prostate.

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Cistectomia radical en tumores vesicales no músculo-infiltrantes que fracasan al tratamiento con bacilo de Calmette-Guérin

Palabras clave:
BCG
Cáncer de vejiga
Cistectomía

R E S U M E N

Objetivos: Evaluar las características y evolución de los pacientes con tumores vesicales no músculo-infiltrantes (TVNMI) sometidos a cistectomía radical por fracaso a la terapia con bacilo de Calmette-Guérin (BCG).

Material y métodos: De 864 cistectomías radicales (CR) realizadas en nuestro centro entre 1989 y 2002, 95 (11%) se indicaron en pacientes que habían recibido tratamiento previo con BCG.

En 62 casos (65,2%) la CR se realizó por presencia de TVNMI recidivado de alto grado o carcinoma *in situ*, a pesar del tratamiento con BCG. En 17 de ellos (27%) la pieza de cistectomía mostró un estadio ≥ pT2. Se consideró que estos pacientes fueron infraestadiados.

En 33 casos (34,7%) la CR se hizo por progresión clínica a enfermedad músculo-infiltrante (≥ T2) durante el seguimiento.

Analizamos las características y evolución de los pacientes cistectomizados por fracaso a la terapia con BCG y si existían diferencias entre los infraestadiados y los que presentaron progresión clínica durante el seguimiento.

Resultados: La supervivencia cáncer-específica a los 5 años fue del 90% en los 45 casos con estadio clínico y patológico de TVNMI, y del 50,6% en los 50 pacientes con progresión a enfermedad músculo-infiltrante (progresión clínica e infraestadiados) ($p < 0,05$). No hubo diferencias en la supervivencia entre los pacientes infraestadiados y con progresión clínica. La mediana de tiempo entre el diagnóstico del tumor y la progresión fue de 24 meses (percentil 10-90; 6-98 meses). Los pacientes con progresión clínica presentaron de forma significativa mayor proporción de tumores T1 ($p = 0,015$) en la RTU previa a la progresión y más pT3 ($p < 0,01$) en pieza de CR. Los pacientes infraestadiados tuvieron más estadios patológicos pT4 ($p < 0,02$).

Conclusiones: En TVNMI de alto riesgo que fracasan a la BCG, la CR debe realizarse antes de la progresión a tumor músculo-infiltrante. Los T1 de alto grado son responsables de la mayor parte de progresiones clínicas y tempranas. Ciertos TVNMI pueden presentar progresión subclínica a través de la próstata.

Introduction

High-grade Ta-T1 urothelial bladder carcinomas and carcinoma in situ (CIS) have a high risk of recurrence and progression to muscle-invasive disease. Most of these non-muscle-invasive bladder tumors (NMIBC) are initially treated with transurethral resection (TUR) and intravesical bacillus Calmette-Guerin (BCG)[1,2] . BCG therapy appears to reduce relapses and progression in high-risk NMIBC[3], but in patients with prolonged follow-up this therapy fails in a considerable percentage of cases[4]. The definition of what constitutes failure of BCG therapy has been controversial. The European Association of Urology recently provided the definition of failure of BCG therapy: presence of high-grade NMIBC at 3 and 6 months post-BCG (though an additional BCG course provides a response in more than 50% of cases), any worsening of disease during BCG treatment and appearance of progression to muscle-invasive disease (=T2). They conclude by indicating that radical cystectomy (RC) is the most appropriate treatment in the event of BCG failure[5].

In high-risk NMIBC, RC should be performed before progression because otherwise survival is significantly decreased[6,7]. Disease progression is usually clinically evident and the patient develops a muscle-invasive tumor diagnosed during follow-up, but it has also been seen that some patients with high-risk NMIBC have a silent progression undetected during follow-up and that may be responsible for an unexpected poor outcome[8,9].

In this scenario, we conducted the study in the patients of our series who underwent RC because they were considered to have failed BCG therapy. We subsequently analyzed the characteristics and outcomes of patients who had invasive tumor (=pT2) in the cystectomy specimen, with the aim of assessing them for possible progression patterns.

Materials and methods

From January 1989 to May 2002, 864 RC were performed in our center for urothelial carcinoma. We conducted a retrospective

study of the clinical histories of 95 patients (11%) with initial NMIBC who underwent RC because they were considered to have failed TUR and subsequent BCG therapy. Sixty-two patients underwent RC due to relapsing, high-risk NMIBC and 33 due to the occurrence of clinical progression (= T2) during follow-up.

Of these, 83 (87.4%) were men and 12 (12.6%) were women, with a median age of 66 years (10-90th percentile, 51-76 years) at the time of RC. All had received at least one BCG cycle (81 mg Connaught strain BCG weekly for 6 weeks) before RC. A re-TUR was not performed in T1 tumors or maintenance BCG therapy given during the study period.

In the 62 (65.2%) cases in which RC was indicated due to relapsing, high-risk NMIBC or CIS after BCG therapy, even though the last TUR before RC showed NMIBC, RC was performed because they were considered to be patients with a high risk of progression to muscle-invasive tumor. Initially, most RC in this group were indicated due to a lack of response to two BCG cycles. Subsequently, high-grade, early recurrence (3-6 months) post-BCG therapy was also an indication for RC. Despite this, the cystectomy specimen showed a stage pT2 or higher tumor in 17 (27%) cases. These 17 patients were considered to have been understaged when their last TUR before cystectomy was performed[7].

In the 33 (34.7%) cases in which RC was done due to progression to muscle-invasive disease (=T2) during post-BCG follow-up, histology of the last TUR before RC already showed a muscle-invasive tumor.

Stratification prior to RC was performed by bimanual palpation under anesthesia, TUR of the bladder tumor and collection of 6 cold cup biopsies from normal-looking mucosa, including one proximal to the verumontanum of the prostatic urethra. Abdominal computed tomography (CT) was performed in most muscle-invasive tumors and bone scans in case of bone pain.

In all cases, RC with lymph node dissection was performed using the standard procedure. RC specimens were analyzed according to European guidelines[10]. Histopathological results were classified according to the TNM system. Cases with prostate stromal involvement by urothelial tumor were considered pT4.

Follow-up after RC was every 4 months for the first year and every 6 months thereafter. A physical examination, blood tests, chest X-ray and ultrasound/abdominal CT were performed at each visit.

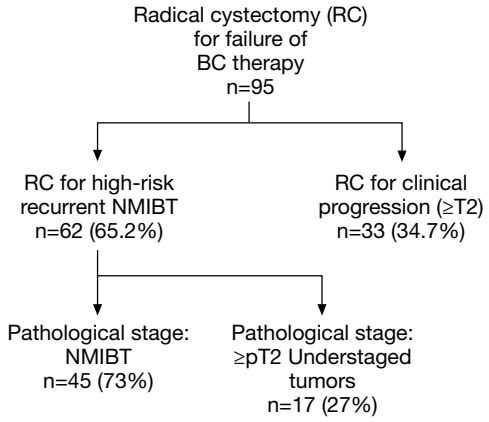

Figure 1 – Radical cystectomy due to failure of bacillus Calmette-Guerin (BCG) therapy. NMIBC: non-muscle-invasive bladder tumor.

We assessed the indications for RC and the characteristics and outcomes of patients with NMIBC who finally underwent RC despite BCG therapy.

The group of 50 patients (33+17) with disease progression was then analyzed separately. This was done to see whether there were differences between the 33 patients who had clinical progression during post-BCG follow-up and the group of 17 understaged patients (Fig. 1) in the time interval between tumor diagnosis and RC, number of TUR and BCG cycles before progression, clinical and pathological stage and outcome.

Statistical analysis was performed using SPSS, version 16.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were analyzed using means, medians, percentiles, and 95%. confidence intervals. The chi-square test was used to evaluate the association between independent categorical variables and Student's t test for quantitative variables. A p-value < 0.05 was considered significant. Survival analysis was done using the Kaplan-Meier method.

Table 1 – Number of bacillus Calmette-Guerin cycles and histology of last transurethral resection of the 62 patients undergoing radical cystectomy for non-muscle-invasive bladder tumors with high risk of progression

Stage	Grade	Number of patients (with CIS)	Number of BCG cycles 1	2	3
CIS		22	8	13	1
Temp	Low	1 (1)	-	-	1
	High	6 (4)	1	5	-
T1	High	31 (11)	19	9	3
Tx	High	2	-	2	-
Total		62 (16)	28	29	5

BCG: Bacillus Calmette-Guerin; CIS: carcinoma in situ.

Table 2 – Number of bacillus Calmette-Guerin cycles and histology of last transurethral resection of 17 understaged patients (stage = pT2 in cystectomy specimen

Stage	Grade	Number of patients (with CIS)	Number of BCG cycles 1	2	3
CIS		4	2	2	-
Temp	High	4 (3)	1	3	-
T1	High	8 (1)	4	4	-
Tx	High	1	–	1	-
Total		17 (4)	7	10	0

BCG: Bacillus Calmette-Guerin; CIS: carcinoma in situ.

Table 3 – Number of bacillus Calmette-Guerin cycles and histology of the last transurethral resection with non-muscle-invasive bladder tumor in 33 patients with subsequent clinical progression

Stage	Grade	Number of patients (with CIS)	Number of BCG cycles 1	2	3
CIS		2	-	2	-
Temp	High	1 (1)	1	-	-
T1	High	28 (16)	18	8	2
Tx	High	2	-	1	1
Total		33 (17)	19	11	3

BCG: Bacillus Calmette-Guerin; CIS: carcinoma in situ.

Results

Tables 1, 2 and 3 show the tumor characteristics and indications for RC in the 62 patients with relapsing, high-risk NMIBC or CIS despite BCG therapy, 17 understaged patients and 33 patients with clinical progression, respectively.

With a mean follow-up after RC of 32.4 months (10th-90th percentile, 5-97 months), five-year cancer-specific survival in the 95 patients who underwent RC due to BCG failure was 67%. Five-year cancer-specific survival was greater in the 45 patients who underwent RC for relapsing, high-risk NMIBC with non-invasive disease in the RC specimen than in the 50 patients who showed disease progression (patients with clinical progression plus understaged patients): 90% versus 50.6%, respectively ($p < 0.05$). There were no significant differences in survival between patients with clinical progression and understaged patients: 53% versus 38%, respectively ($p = 0.4$) (Figs. 2 and 3).

Overall assessment of the 50 patients (33+17) with disease progression (= pT2 in cystectomy specimen) revealed that 14 (28%) had organ-confined tumors and 36 (72%) had extravesical disease. The median time from tumor diagnosis to tumor progression was 24 months (10th-90th percentile, 6-98 months).

Table 4 shows the differences between the 33 (66%) patients with clinical progression and 17 (34%) understaged patients.

Patients with clinical progression had a significantly more T1 tumors in TUR before progression ($p = 0.015$) and also fewer TUR before progression ($p = 0.0002$). In 64% of T1 tumors in this group, progression was seen at three months.

Pathological examination of the RC specimen showed that patients with clinical progression more often had pT3 tumors ($p < 0.01$) and understaged patients had more pT4 stages ($p < 0.02$). Ten (66%) of 15 men among the 17 understaged patients had prostate stromal involvement by tumor (7 pT4 and 3 N+ also with prostate stromal involvement).

Discussion

If a high-risk NMIBC has a high-grade non-muscle-invasive recurrence after BCG, the possibilities of action are reduced because in the event of subsequent progression (=T2) survival decreases drastically. In these patients, a balance should be sought between being too aggressive and providing curative treatment too late[11].

If a patient with NMIBC who fails BCG therapy undergoes RC when the tumor has a non-invasive clinical and pathological stage, a 5-year survival of 85-95% can be achieved, as in our series[7,12,13]. But if RC is performed for disease progression (=T2), results are not as favorable. Scherier et al[14] compared a group of 74 patients with NMIBC treated with BCG and subjected to RC for progression (=T2) with 89 patients

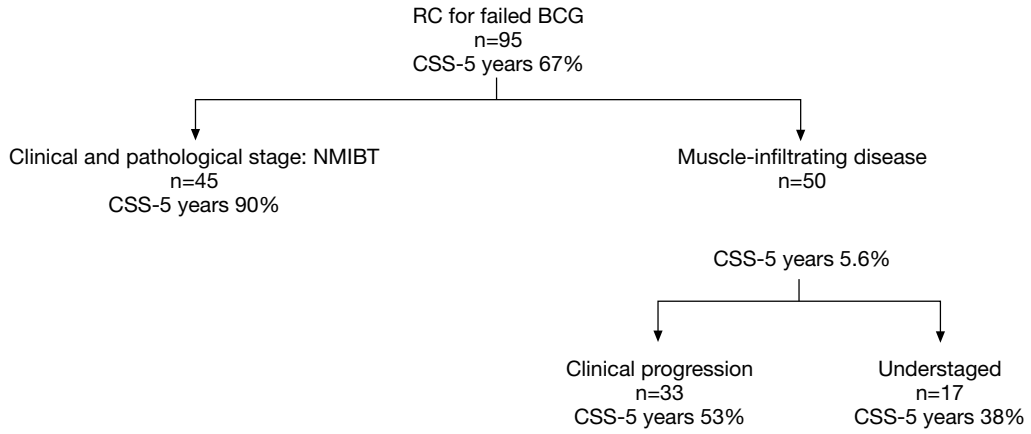

Figure 2 – Five-year cancer-specific survival (CSS) in the different patients groups. BCG: Bacillus Calmette-Guerin; RC: radical cystectomy; NMIBC: Non-muscle-invasive bladder tumor.

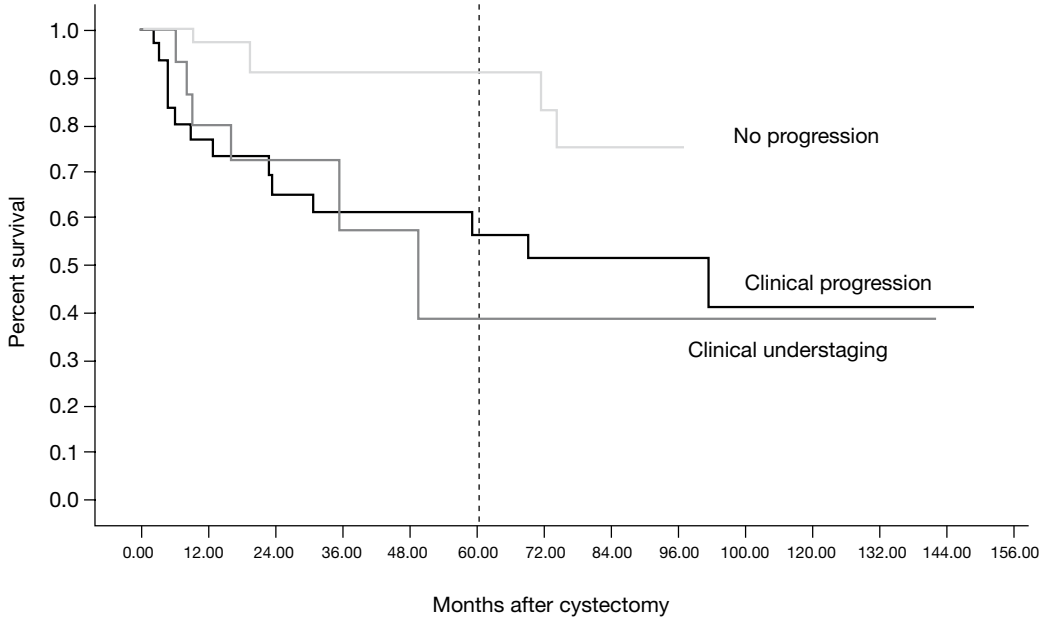

Figure 3 – Kaplan-Meier curves comparing survival between patients with clinical and pathological stage of non-muscle invasive bladder tumor (no progression), patients with clinical progression and understaged patients.

cystectomized due to a primary muscle-invasive tumor. Five-year cancer-specific survival was 28% in the first group and 55% in the second (p = 0.0015), differences not observed by other authors[15,16]. Recently, Lerner et al[17] and Nieder et al[12], also in patients with NMIBC treated with BCG and subjected to RC for disease progression (=T2), found a 5-year cancer-specific survival of 44% and 74%, respectively. In our study, survival in this group was 53% (group with clinical progression). These results reaffirm that in patients with NMIBC who fail BCG therapy, survival is significantly decreased if RC is performed for progression.

Another objective of our study was to evaluate whether there were differences between patients who showed clear progression during follow-up (clinical progression) and those in whom progression was not detected during follow-up or in TUR before RC, but in the cystectomy specimen (understaged patients).

There are numerous historical studies analyzing understaging in NMIBC subjected to RC, but very few do so only in patients treated with BCG. In this situation, understaging ranges from 27% to 52%[7,12,18]. In general, this is greater in T1 tumors in case of multifocality, CIS, absence

Table 4 – Clinical and pathological differences between patients with clinical progression and understaged patients

Characteristics of the tumor before progression	Clinical progression; n=33 (%)	Understaged; n=17 (%)	P-value
= 2 TUR	14 (42)	17 (100)	p = 0.0002
= 2 BCG cycles	14 (42)	10 (58)	p = 0.43
cT1	28 (84)	8 (47)	p = 0.015
Pathological subgroups			
Organ-confined pT2	9 (28)	5 (29)	p = 0.85
Extravesical	24 (72)	12 (71)	p = 0.79
pT3	14 (42)	1 (5.8)	p< 0.01
pT4	3 (9)	7 (41)	p< 0.02
pN+	7 (21)	4 (24)	p = 0.84
Mean time to progression (months)	26	36	p=0.18
5-yr CSS	53%	38%	p=0.41

BCG: bacillus Calmette-Guerin; TUR: transurethral resection; CSS: cancer-specific survival.

of muscle in the TUR sample, involvement of the prostate urethra and radiological suspicion of invasive tumor[7,19,20].

In our study, we found that the group of 33 patients with clinical progression had a significantly greater proportion of T1 tumors in TUR before progression, fewer TUR, a trend to receive fewer BCG courses and also to have a shorter interval between diagnosis and progression. This confirms that in NMIBC, high-grade T1 tumors may have early clinical progression. In 18 (64%) of 28 patients with T1 tumors, clinical progression occurred three months after the last TUR. This progression at three months and the high proportion of pT3 tumors observed in the cystectomy specimen could be explained by possible tumor persistence or understaging in TUR before progression.

On the other hand, the 17 understaged patients proved to be a highly heterogeneous group. In TUR before progression, the same number of cases was seen with CIS and Ta tumors as T1 tumors. These patients were more often indicated TUR, tended to receive more BCG courses and also had a longer interval between diagnosis and occurrence of muscle-invasive disease. That is, another group of NMIBC may be identified, perhaps with less initial aggressiveness, and therefore subjected for a longer period to more conservative treatments with TUR and BCG. A group of tumors that would have an unexpected progression not detected until pathological examination of the RC specimen. Unlike the group of patients with clinical progression, in the group of understaged patients the percentage of prostate stromal involvement in the RC specimen was greater (66% including male patients only). We can thus affirm that in most of the group of 17 understaged patients progression was not due to possible tumor persistence after an incomplete TUR; but because of subclinical prostate involvement by urothelial carcinoma (undetected when TUR was performed). This possibility of prostate stromal involvement in NMIBC with long follow-up has also been reported by other authors[8].

By identifying these two possible forms of progression (clinical and subclinical within the prostate), our results confirm that there are two significant issues in the management of high-risk NMIBC. The first and key issue to try to prevent potential clinical progression is TUR (mainly in T1 tumors). A TUR in which tumor persistence and understaging should be combated to prevent an early progression at 3 months (first follow-up cystoscopy). Because of the possibility of tumor persistence and understaging in high-grade T1 tumors, both US[21] and European guidelines[5] currently recommend repeat TUR before starting BCG. We did perform a repeat TUR in high-grade T1 tumors during the study period. A re-TUR might have detected an invasive tumor in some cases in our series and changed the therapeutic approach. However, we previously reported a progression rate of 5% at 3-6 months[22] and overall progression rate of 15.7% in BCG-treated T1 G3 tumors (unpublished results), while the progression rate in BCG-treated CIS patients was 19%[23]. This means that a very large percentage of high-risk NMIBC responded to BCG therapy, and that the rate of understaging without a re-TUR was actually low in our center.

The second and also important issue (though it involves a smaller patient group) is the need to perform biopsies of the prostatic urethra in follow-up of high-risk NMIBC to detect the presence of a tumor at this level, and so prevent unexpected subclinical progression. A biopsy that should be performed even in the absence of macroscopic lesions. The difficulty in performing correct endoscopic staging of the true prostatic involvement by urothelial tumor is known. Patients with no macroscopic tumor, with papillary lesions or CIS in the prostatic urethra, as well as those with tumors involving the prostatic ducts, may have stromal involvement stromal in the RC specimen[7]. With regard to the performance of prostatic urethra biopsies, the European guidelines recommend them in bladder neck tumors, when CIS is present or suspected, and when macroscopic abnormalities are visible in the prostatic urethra. These biopsies should be taken close to the verumontanum and using a resection loop[5].

One of the limitations of our study was not having the total number of patients treated with BCG in the study period. This would have helped to show that the patients analyzed in our series were a group of highly selected NMIBC: those

with the poorest outcome. Similarly, the natural history of BCG-treated NMIBC may be highly variable, so we cannot be conclusive with the number of patients in our series, but can suggest that two possible forms of progression were identified: clinical and subclinical progression.

What is essential is to identify patients with NMIBC at high risk of progression and provide them with radical treatment at the optimal time. An important reflection is that despite following accepted BCG treatment regimens and indications for RC during the study period, 50 of the 95 RC performed due to BCG failure had muscle-invasive disease, and, of these, half had an unfavorable outcome.

The study period of our paper (1989-2002) coincided with the publication of the first long-term results of BCG treatment, and thus also with possible indications for RC in these patients. These indications for RC have expanded over time and tended to increasingly early interventions. At present, many authors are in favor of performing RC as initial therapy in high-risk T1 tumors[24].

In order to improve our results in the treatment of this complex group of tumors, we presently perform: A re-TUR in patients with T1b-c or extensive T1 tumors, BCG induction and maintenance to 1 year, prostatic urethra biopsies by resection during follow-up of high-risk patients and RC for BCG failure increasingly earlier, in accordance with European guideleines[5]. We have also recently seen that ezrin expression in NMIBC cells may predict future development of muscle-invasive disease and, therefore, be a useful marker of progression[25].

Conclusions

In patients with high-risk NMIBC who fail BCG therapy, RC should be performed before progression to muscle-invasive tumor. Otherwise, survival is significantly decreased. In NMIBC treated with BCG, high-risk T1 tumors are responsible for most clinical and early progression. Patients with NMIBC may have subclinical progression, mainly within the prostate.

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