SURVIVAL AFTER CURATIVE TREATMENT OF MUSCLE-INVASIVE BLADDER CANCER

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This retrospective study includes 534 patients who had curatively intended treatment for T2/T3/T4a bladder cancer at the Norwegian Radium Hospital during the period 1980–1990. Total cystectomy preceded by preoperative radiotherapy represented the treatment of choice in 263 patients (CysGr). High-dose radiotherapy was applied in 271 patients in whom total cystectomy could not be performed (RadGr). From 1985 neo-adjuvant cisplatin-based chemotherapy was increasingly used. The 5-year crude survival rate for all patients was 35% with 40% for CysGr and 22% for RadGr. In CysGr the 5-year survival rate was highest (63%) for patients with <pT2 and lowest for pN+ patients (13%). The following independent prognostic parameters were identified for the total group: T category, trial participation, treatment, creatinine, haemoglobin, age and time since initial diagnosis. No significant difference in survival was found when comparing the treatment results obtained before and after 1985. In spite of the introduction of multimodality therapy the treatment results for T2/T3/T4a bladder cancer have remained unchanged. However, subgroups of patients may benefit from this approach allowing bladder conservation in selected cases. More effective adjuvant regimens have to be developed for high-risk patients (pT3b/pN+).

Yearly, about 1 000 new cases of bladder cancer are diagnosed in Norway and 25% of these have histologically verified muscle invasion (≥T2) (1) at the time of primary diagnosis. Although there is no national consensus on the treatment of these patients, oncological multimodal therapy is often considered. In 1985 about 50% of all patients from Health Region II with newly diagnosed ≥T2 bladder cancer were thus referred to the Norwegian Radium Hospital (NRH) (2).

The aim of the present report was to analyse the outcome of patients with muscle-invasive bladder cancer who during the years 1980 to 1990 had been referred to the NRH and in whom curative multimodality treatment had been planned. The analysis represents an up-date of previously published results (3, 4) including a few additional patients who were identified by repeated review of the medical records.

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Material and Methods

Patients

A retrospective review of the patients' medical records identified 534 patients from the NRH who fulfilled the following eligibility criteria: 1) start of curatively intended multimodality treatment for muscle-invasive bladder cancer between 01/1980 and 01/1991, including either total cystectomy or pelvic high-dose radiotherapy, 2) T2/T3/T4a bladder cancer (1), based on clinical T categorization, 3) no evidence of metastases at the start of treatment based on liver function tests, chest x-ray and bone scan, and 4) no major somatic or psychological morbidity.

Included in the study were 373 patients (70%) from Health Region II and 161 patients (30%) from other parts of Norway. Owing to increasing regionalization of the Norwegian Health Care Service the percentage of patients from health regions other than Health Region II decreased from 40% (1980–1983) to 9% (1989–1990).

Treatment

The choice of treatment was left to the urologist's discretion, with no randomisation between total cystectomy and high-dose radiotherapy. During the inclusion period total cystectomy preceded by preoperative pelvic radiotherapy represented the first choice of curatively intended treatment of muscle-invasive bladder cancer at the NRH. Total cystectomy was performed at the NRH or at a county hospital by the referring urologist, the choice depending on the patient's request and the hospital's facilities. At laparotomy, the iliac obturator glands were exposed and a formal staging lymphadenectomy was performed. In women the urinary bladder, the urethra and the anterior vaginal wall were resected en bloc, and in men the urinary bladder was removed together with the prostate and the seminal vesicles. Enlarged lymph nodes were removed. If frozen sections showed metastatic growth, cystectomy was omitted based on the surgeon's decision. Urinary diversion was carried out according to the principles of the individual clinics.

Preoperative radiotherapy was applied by two schedules: 46–50 Gy in 2 Gy fractions over 4.5–5 weeks (early 1980s) or 20 Gy in 4 Gy fractions in one week (increasingly from 1982). This irradiation was given to anterior and posterior opposing pelvic fields including the bladder and the pelvic lymph nodes.

High-dose radiation therapy

High-dose radiotherapy was principally given if cystectomy was refused by the patient, or if the patient was judged inoperable, usually due to significant co-morbidity or advanced T category. Curatively aimed high-dose radiation therapy of bladder cancer implied irradiation at a nominal standardized dose (NSD) of at least 1 700 ret and preferably 1 750 ret. Two principal fractionation schedules and treatment schedules were applied. During the first 4 years of the study, 2.35 Gy was given daily four times per week up to a total dose of 56.4 Gy. The first 16 fractions were given to opposing anterior and posterior pelvic fields reaching from the lower edge of the obturator foramina to the L5/S1 intervertebral disc. Each field was treated on alternative days. Thereafter the target volume was reduced, including the bladder only, and treatment was delivered by a three-field technique, the patient lying in the supine position (two oblique anterior and one posterior field, each field treated daily).

From 1984, the four-field box technique was increasingly used (one anterior, one posterior and two lateral fields). The target volume encompassed the bladder and, if present, any extravesical tumour growth based on clinical and CT findings. A safety margin of 2 cm outside the bladder was recommended. The patients received 2 Gy daily five times per week by 30 fractions (total dose 60 Gy). In patients older than 75 years of age, 1.8 Gy was given daily for 35 fractions (total dose 63 Gy). Each field was treated daily. Treatment was given with the patient in supine position.

Chemotherapy

Neo-adjuvant cisplatin-based chemotherapy was increasingly used, initially as a feasibility study or within several phase II studies. From 1985 the NRH participated in two international randomized phase III trials evaluating neo-adjuvant chemotherapy: Nordic Cystectomy Trial I (1986–1989, 59 patients) (5) and MRC/EORTC Intercontinental Trial (start: 11/1989, 24 patients) (6).

Follow-up

All patients were seen at the NRH 3 months after treatment. Thereafter, the patients were principally followed by the referring urologist every 3–6 months. The choice of investigation at each follow-up was left to the responsible urologist. All patients were followed up until death or for at least 5 years. The median observation time for surviving patients was 110 months (range 61–191).

Statistics

Standard statistical procedures were applied using the SPSS-PC statistical package. Crude survival calculated from start of treatment was used as the principal outcome parameter. Survival was calculated by the Kaplan-Meier method with the logrank test to assess differences. Survival analyses based on pretreatment parameters were made according to the 'intention to treat' principle. Independent prognostic parameters were identified by the forward Cox regression analysis. A p-value of <0.05 was regarded as statistically significant.

Results

Patient characteristics

Two hundred and sixty-three patients were allocated to total cystectomy (CysGr) (Table 1) and 271 patients to high-dose radiotherapy (RadGr). The percentage of patients receiving high-dose radiotherapy remained between 40 and 60% during the 11 years of the study (not shown). Thirty-one patients did not undergo the planned cystectomy, and 8 patients did not complete the scheduled radiotherapy. Preoperative radiotherapy was finally omitted in 2 patients who had been treated with high doses of doxorubicin during their neo-adjuvant combination chemotherapy. Peroperatively detected technical inoperability or regional lymph node metastases were the most frequent reasons for not continuing with cystectomy, whereas unacceptable toxicity was the principal reason for

Table 1

Patient characteristics

	Cystectomy CysGr	Radiotherapy Rad Gr	Total
Number of patients	263	271	534
Number of patients not completing planned treatment	31	8	39
Males/females	204/59	209/62	413/121
Age (years) at treatment start[1]	64[2] (33–80)[3]	73 (32–89)	68 (32–89)
Months since initial diagnosis[1]	3 (0–221)	4 (0–207)	4(0–221)
T category[1]			
T2	110	70	180
T3	145	160	305
T4a	8	41	49
Co-morbidity[1]			
Cardiovascular/pulmonary	48	99	147
Other	58	65	123
No	157	107	264
Performance status[1]			
0	237	172	409
1	24	78	102
2	1	20	21
3	1	1	2
Neo-adjuvant chemotherapy[1]			
CMV[4]	8	1	9
Cisplatin/Doxorubicin	34	1	35
Other	37	43	80
No	184	226	410
Haemoglobin (g/dl)	12.9 (8.6–19.0)	13.0 (7.6–16.8)	13.6 (7.6–19.0)
Creatinine (μmol/l)[1]	92 (35–180)	97 (60–492)	94 (35–492)
Allocated target dose (Gy)			
20 Gy	201		201
40–50 Gy	62		62
50–60 Gy		94	94
$\geqslant$60 Gy		177	177

[1] $p < 0.001$ (between CysGr and RadGr) [2] Median [3] Range [4]Cisplatin/Methotrexate/Vinblastine

premature discontinuation of high-dose radiotherapy. There was no age difference between the two therapeutic groups. However, significantly fewer cystectomy patients presented with co-morbidity. The former patients also had a more favourable distribution of their performance status and of their T category than patients from RadGr ($p < 0.001$). One hundred and twenty-four patients received neo-adjuvant chemotherapy, 43 of these within a randomized trial. Neo-adjuvant chemotherapy (any type) was given more often to patients scheduled for cystectomy (79 patients) than for radiotherapy (45 patients) ($p < 0.001$).

Survival

The 5-year crude survival rate for all patients was 35%, for cystectomy patients 48% and for radiotherapy patients 22% (Fig. 1). The corresponding median survival times were 2.4, 4.5 and 1.8 years, respectively. In general, for each T category the survival rate after cystectomy was twice that following radiotherapy (Fig. 2). For both treatment modalities patients with T3 tumours had a significantly poorer prognosis than those with T2 tumours.

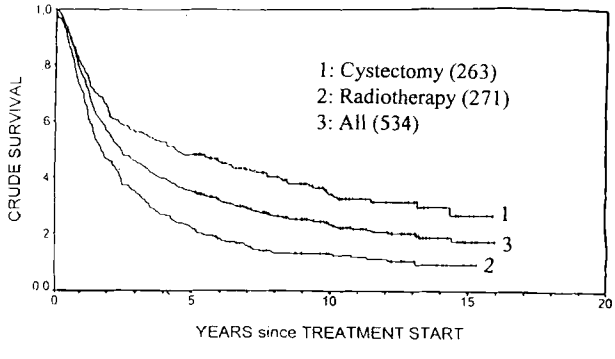
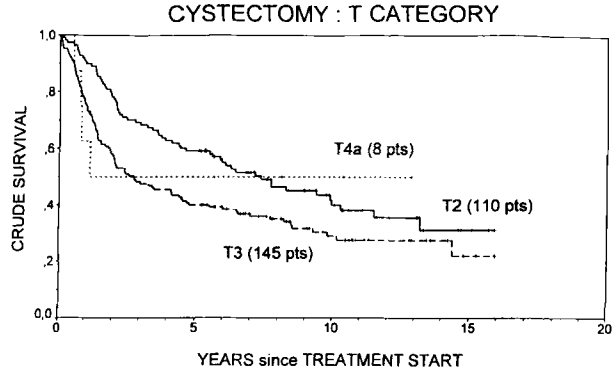


Fig. 1. Crude survival after curatively intended treatment of patients with T2/T3/T4a bladder cancer (NRH, 1980–1990), total group, cystectomy group and radiotherapy group



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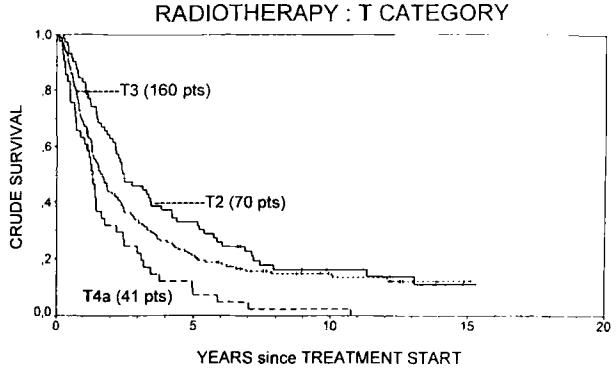

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Fig. 2. Survival and T category A: Cystectomy group B: Radiotherapy group

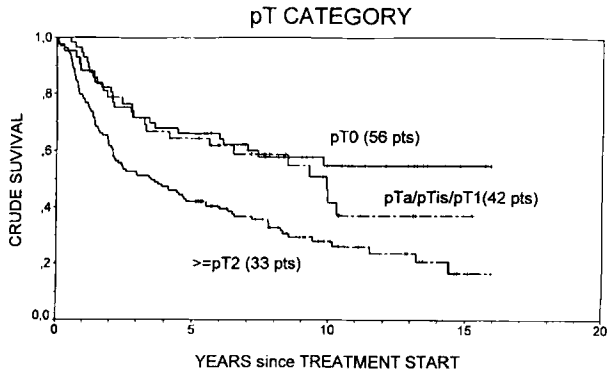

Fig. 3. Survival and pT category

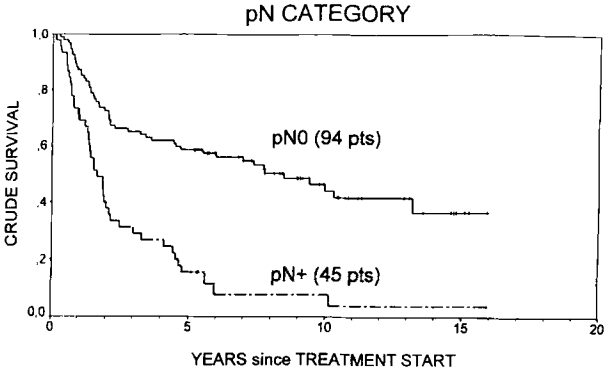

Fig. 4. Survival and pN category

However, it was only for RadGr patients that the T4a category was associated with decreased survival.

For patients in the cystectomy group both the pT category (pT0 vs pTa/pTis/pT1 vs ⩾pT2, Fig. 3) and the pN category (pN0 vs pN+, Fig. 4) significantly predicted crude survival (median survival in years: pT0: not reached; pT0/pTis/pT1: 9.9; ⩾pT2: 3.5; pN0: 8.4; pN+: 1.7). Patients in whom no tumour was found in the cystectomy specimen (pT0), or in whom the tumour was 'down-staged' (pTa/pTis/pT1) had a 63% 5-year survival. A more detailed analysis of evaluable patients with ⩾pT2 tumours revealed the following figures for 5-year and median survival, respectively: pT2: 68%, 7.7 years; pT3a: 46%, 4.7 years: pT3b: 29%, 2.5 years. In patients where lymph node metastases were detected at surgery (32% of the patients with lymph node histology), the 5-year survival rate was only 13%.

The results of univariate survival analyses for all 534 patients, are summarized in Table 2. Crude survival was related to the treatment modality, T category, patient's age, performance status, co-morbidity, time elapsed since initial diagnosis and the serum levels of haemoglobin and creatinine. Patients entered into one of the 2 trials evaluating neo-adjuvant chemotherapy displayed a significantly superior survival rate compared with that of non-trial

Table 2

Univariate survival analysis, all 534 patients

Parameter	Categories	Median survival (years)	p-value
Age (years)	<70	3.6	<0.001
	⩾70	1.9	
Gender	Males	2.4	0.34
	Females	2.5	
Treatment	Cystectomy	4.5	<0.001
	Radiotherapy	1.8	
Trial	Yes	7.7	<0.001
	No	2.2	
T category	T2	4.4	<0.001
	T3	2.0	
	T4	1.3	
Haemoglobin (g/dl)	<12.0	1.7	<0.001
	⩾12.0	3.0	
Creatinine (μmol/l)	⩽120	3.0	<0.001
	>120	1.3	
Performance status	0	2.9	<0.001
	⩾1	1.5	
Co-morbidity	No	3.0	0.002
	Yes	4.1	
Months since initial diagnosis	⩽12	2.8	0.004
	>12	2.0	
Years of treatment	1980/85	2.2	0.19
	1986/90	2.0	

Table 3

Multivariate Cox survival analysis

	Relative death risk	95% CI[1] relative death risk	p-value
All patients n = 534			
T3 vs. T2	1.3	1.0–1.7	<0.05
T4a vs. T2	1.7	1.2–2.4	<0.01
Trial: No vs. Yes	1.6	1.1–2.3	<0.05
Treatment: Rad[2] vs. Cyst[3]	1.4	1.1–1.8	<0.01
Creatinine (≥120 vs. <120 μmol/l)	1.5	1.1–1.9	<0.01
Haemoglobin (<12.0 vs. ≥12.0 g/dl)	1.4	1.1–1.8	<0.01
Age (≥70 vs. <70 years)	1.4	1.1–1.7	<0.01
Interval (≥12.0 vs. <12.0 months)	1.4	1.1–1.7	<0.05
Cystectomy n = 263			
T3 vs. T2	1.6	1.1–2.2	<0.01
T4a vs. T2	1.1	0.4–3.0	NS[4]
Trial: No vs. Yes	1.6	1.1–2.3	<0.05
Haemoglobin (<12.0 vs. ≥12.0 g/dl)	1.4	1.0–2.0	<0.05
Perf. status (≥1 vs. 0)	1.7	1.0–2.7	<0.05
Radiotherapy n = 271			
T3 vs. T2	1.2	0.9–1.6	NS
T4a vs. T2	1.8	1.2–2.6	<0.01
Haemoglobin (<12.0 vs. ≥12.0 g/dl)	1.5	1.1–2.0	<0.01
Creatinine (≥120 vs. <120 μmol/l)	1.5	1.1–2.0	<0.01
Age (≥70 vs. <70 years)	1.5	1.1–2.0	<0.01
Interval (≥12 vs. <12 months)	1.4	1.0–1.9	<0.05
Concom.dis.: Yes vs. No	1.4	1.0–1.8	<0.05

[1] Confidence interval [2] Radiotherapy [3] Cystectomy [4] Not significant

patients. The year of treatment or the patients' gender had no impact on survival. No survival difference was observed for the different schedules of precystectomy irradiation and high-dose radiotherapy (data not shown).

All pretreatment parameters which in the univariate analysis displayed a p-value of $p < 0.01$ were included in the multivariate analyses performed for all patients and separately for CysGr and RadGr (Table 3). The treatment modality and trial participation proved to be significantly independent prognostic factors if all 534 patients were considered, together with the T category, age, serum level of creatinine, haemoglobin and the time since initial diagnosis. If CysGr and RadGr were analysed separately, the level of haemoglobin and the T category remained independent prognostic factors, though the impact of the T category differed for the treatment groups: In CysGr (but not in RadGr) discrimination between T2 and T3 was of prognostic significance. Compared to the T2 category, the T4a category was related to reduced survival in RadGr, but not in CysGr patients. Trial participation and performance status were additional independent prognostic factors for cystectomized patients. Except for T category the outcome after radiotherapy was independently related to the patient's age, co-morbidity, the serum creatinine level and the time elapsed since initial diagnosis.

Discussion

An increasing percentage of today's cancer patients enquire about survival rates in general and about the responsible institution's treatment results in particular, when treatment decisions have to be made during patient counselling. This is the background of the present analysis. Whereas we previously have reported cancer-related survival rates after observation times of <5 years (3, 4), we now present definite 5-year crude survival rates. Though a few deaths may have been due to concomitant diseases, muscle-invasive bladder cancer is considered to be the reason for lethal outcome in the overwhelming majority of the patients (2). We therefore consider crude survival to be a clinically valid outcome parameter in these patients.

Our series cannot serve as a basis for comparison between total cystectomy and high-dose radiotherapy in the treatment of muscle-invasive bladder cancer as no randomization has been performed. In particular, during the 1980s total cystectomy was considered to be the treatment of choice in Norway. Definite radiotherapy was applied only if radical surgery was impossible because of advanced age, decreased performance status, severe co-morbidity or a large primary tumour. Many institutions have used and still apply similar selection criteria for cystectomy versus radiotherapy, though no randomized trials exist which

evaluate the role of cystectomy versus radiotherapy in these patients, except for a phase III study from 1982 by Bloom et al. (7). This trial showed that patients <60 years old fared significantly better when treated with preoperative radiotherapy (40 Gy) and total cystectomy than with irradiation alone. In patients aged 60–64 years there was a non-significant trend in favour of cystectomy, and in patients over 65 years of age there was no difference in survival.

Many urologists and oncologists have felt the need for new strategies in the treatment of muscle-invasive bladder cancer, including multimodality therapy. The first approach was the introduction of precystectomy pelvic radiotherapy. Based on historical series from the Memorial Sloan Kettering Cancer Center (8), but never shown in randomized trials, precystectomy radiotherapy in the 1970s was claimed to decrease the rate of local recurrence and to increase survival, independently of the target dose. These observations led to the routine use of precystectomy radiotherapy at the NRH early in the 80s. Not all subsequent investigations have been able to confirm survival benefit after precystectomy radiotherapy, and many urological units have now discontinued the use of preoperative irradiation (9). The application of precystectomy radiotherapy (20 Gy) has, on the other hand, not been combined with major medical or administrative problems at the NRH. In view of a possible benefit in terms of reduced risk of pelvic recurrence, we have continued to apply 20 Gy before cystectomy for muscle-invasive bladder cancer, though more recent publications indicate that higher preoperative target doses may be preferable (10).

Our survival rates for the CysGr are comparable with published observations, which are based on clinical T category (11–14). In agreement with other series, we also demonstrate the decreasing survival rates with increasing pT and pN categories (14–17). Patients with ⩾pT3 and pN+ tumours are clearly in need of improved treatment options.

The NRH results for RadGr seem to be slightly inferior to those published from large radiotherapy units, mainly due to the above second priority selection of patients with deeply infiltrating large tumours (18–21). One may further argue that higher target doses (NSD >1 750 ret) would have resulted in improved survival rates. Using conformal radiotherapy techniques, target doses of 64–68 Gy can today be applied with possible increase of the local control rate. Intra-operative (22), interstitial (23) or hyperfractionated (24) irradiation may also facilitate higher target doses and improved tumour control without increased risk of normal tissue damage. The complete eradication of malignant cells from the bladder is an important goal of radiotherapy as this event is related to improved survival (3). In the present analysis we have not discriminated between T3a and T3b tumours, a discrimination which previously has been shown to be of prognostic significance (25). Thus, palpable extravesical tumour growth (T3b) was associated with poor outcome within the first 5 years after radiotherapy.

Muscle-invasive bladder cancer should principally be viewed as a systemic malignancy, similar to stage II breast cancer. Thus, in most patients the condition requires local treatment combined with effective systemic treatment, applied early, in order to eradicate micrometastases. The next attempt to improve survival rates was therefore to introduce neo-adjuvant cisplatin-based chemotherapy in the treatment of muscle-invasive bladder cancer, based on reports of response rates of 50–70% in metastatic disease, with complete response rates of 25% (26–28). Several large multicentre studies of neo-adjuvant chemotherapy were thus started (5, 6, 29). However, in 1996 the routine application of neo-adjuvant chemotherapy in unselected patients with ⩾T2 bladder cancer has become more debatable. Though subgroup analysis of the Nordic Cystectomy Trial I (13) indicated an improved survival in patients with T3/T4a tumours receiving moderate doses of cisplatin and doxorubicin, no superiority of the cisplatin/methotrexate/vinblastine combination could be detected in the MRC/EORTC intercontinental neo-adjuvant trial when all patients are considered. At present the clinician can therefore not claim any advantage of cisplatin-based chemotherapy when counselling a patient with muscle-invasive bladder cancer.

The survival rates from the present series do not indicate any improvement during the 1980s in spite of the increasing attempts to apply multimodality treatment. Subgroup analyses should be done in the large trials to identify pretreatment factors which predict chemotherapy efficacy. Based on such investigations future clinical studies have to deal with patients in whom bladder conserving treatment represents a reasonable alternative to total cystectomy (30). New and more effective drugs have to be developed and investigated in clinical studies, such as paclitaxel (31) or gemcitabine (32). The role of post-operative adjuvant chemotherapy for high-risk groups (pN+, pT3b) has to be evaluated. Preliminary results from relevant trials are highly promising (33). Large international trials will be necessary to obtain rapid and valid results.

In summary, total cystectomy as the treatment of choice and high-dose radiotherapy as second priority therapy in patients with muscle-invasive bladder cancer result in an overall 35% 5-year survival rate (cystectomy: 48%, radiotherapy: 22%). Important prognostic factors are T category, haemoglobin, serum creatinine, age, performance status, co-morbidity and the time elapsed since initial diagnosis. Precystectomy radiotherapy and/or neo-adjuvant chemotherapy has not improved these survival rates. Future subgroup analyses may, however, identify patients with a possible benefit from the multimodality approach in terms of bladder conservation. The identification of such subgroups and the development of more effective multimodality treatment of muscle-invasive bladder cancer remain issues of future international uro-oncological research.

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