

UDC: 616-006.62

N.S. NURGALIEV<sup>1</sup>

<sup>1</sup>Kazakh Institute of Oncology and Radiology, Almaty, the Republic of Kazakhstan

## Critical analysis of diagnostics and treatment of patients with bladder cancer in the Republic of Kazakhstan

**Relevance.** The incidence of bladder cancer (BC) in the Republic of Kazakhstan over the past years remains at a stable level of about 4.0% per 100,000. BC ranks 10 and is more common in men. Mortality was declining over the past ten years and amounted to 1.2% per 100,000 in 2016. The national cancer registry shows an increasing number of patients detected early. The detection at stages I and II exceeds 70% while it is well known that it is necessary to distinguish these two stages since they have a completely different prognosis and treatment tactics. About 4-5% of patients are identified at stage IV whereas the annual mortality from this nosology is about 15% what evidences incorrect staging.

**Results.** The coverage of treatment in recent years has exceeded 90%. Still, in some cases the protocols of diagnostics and treatment are not followed and therefore a part of patients does not receive radical treatment in full scope. The number of radical cystectomies that are considered to be the gold standard for treatment of muscle-invasive bladder cancer is growing. Still, 1/4 of these operations is palliative. The share of radiation treatment which is not a standard treatment for BC is relatively high.

**Conclusions.** A critical view on the provided treatment of this pathology is required to improve the current situation.

**Keywords:** bladder cancer, morbidity, mortality, muscle-invasive bladder cancer treatment methods.

**Relevance.** Bladder cancer (BC) ranks 9<sup>th</sup> among all malignant neoplasms globally. In 2012, over 380,000 new cases of BC were registered worldwide, with over 150,000 deaths from BC [1]. The non-muscle invasive bladder cancer (nmIBC) accounts for about 75% of all newly diagnosed BC cases. At early detection, nmIBC can be successfully treated with a relatively favourable prognosis. However, up to 40% of nmIBC patients will have a recurrence of the disease in a near-term prospect, and 10-20% will have the disease progression to muscle-invasive BC (miBC). miBC accounts for a much higher mortality (about 50%), so its early detection is of crucial importance. In case of nmIBC, radical cystectomy (removal of bladder) or its combination with chemotherapy is recommended [1].

**Aim of the study** is to assess the current situation of BC detection and mortality, as well as the adequacy of treatment provided in the Republic, especially with regard to miBC. Tasks of the study: to perform the analysis of diagnostics and treatment of this disease in the recent years.

**Materials and Methods.** The study focused on the updated "Reports on malignant neoplasm diseases" and

"Reports on malignant neoplasm patients" (Forms No.7 and No.35 approved by the Order No.128 of the Minister of Health of the Republic of Kazakhstan dated March 6, 2013) for the years 2005-2016 (continuous sampling), and the data from the "Notification about the patient with newly diagnosed cancer or other malignant neoplasm" (Form No.090/y approved by the Order No.514 of the acting Minister of Health of the Republic of Kazakhstan dated July 31, 2012). The data was reviewed for the whole country and taking into account the administrative-territorial division – 14 oblasts and 2 cities of republican significance, Astana and Almaty. The annual analytical reports "On oncological service status" submitted by the oncological dispensaries for the period 2005-2016 have also been reviewed.

**Results and Discussion.** During 10-year follow up, over 6,460 newly detected cases of BC were registered in Kazakhstan. According to the National Cancer Registry, over 600 new cases of BC are detected annually (about 4.0 per 100 thousand) [2-5] (Table 1).

**Table 1** – Overall statistical rates of BC morbidity and mortality in the Republic of Kazakhstan, 2005-2016

Year	Registered, abs.	Newly detected		Rank			Died	
		abs.	per 100 thousand	both sex	Men	Women	abs.	per 100 thousand
2005	2392	623	2.1	15	10	19	376	2.2
2006	2549	608	2.1	15	10	19	328	1.9
2007	2691	609	3.9	17	10	19	316	2.0
2008	2840	600	3.8	15	11	19	329	2.1
2009	2983	623	3.9	17	10	19	349	2.2
2010	3161	586	3.6	17	12	19	291	1.8
2011	3298	628	3.8	18	9	19	306	1.8
2012	3185	656	3.9	18	10	19	316	1.9
2013	3266	642	3.8	18	11	19	273	1.6
2014	3281	694	4.0	18	10	19	283	1.7
2015	3402	687	3.9	18	10	20	248	1.4
2016	3586	736	4.1	19	10	20	215	1.2

According to statistical data, since 2005 the BC incidence has grown in absolute figures, however, there was no significant growth per 100,000 due to the recorded annual population growth. However there is a slight growth trend of the incidence in the recent years. Still, the number of registered patients with BC is growing (from 2,392 patients in 2005 to 3,586 in 2016) what evidences a higher efficiency of treatment of this category of patients.

BC is not a common cancer pathology. In 2005-2008, it ranked 15th vs. 19th position in 2016. It also indicates a no growth trend of that cancer nosology. Women suffer less from this disease globally; there is 1 woman with BC per 3-4 men with BC. In men, BC is in Top-10 cancer pathologies. It stably ranks 10th with minor fluctuations by years (see Table 2) while in women BC ranks 19-20<sup>th</sup>.

**Table 2** – Staging, annual mortality and 5-year survival of BC patients

Year	Stage			Annual mortality	Correlation between annual mortality and stage IV	5-year survival
	I-II	III	IV			
2005	56.0	37.3	6.7	No data	No data	37.4
2006	55.2	38.8	6.0	-	-	37.3
2007	59.5	34.2	6.3	23.4	3.9	38.8
2008	57.3	36.2	6.5	23.1	3.7	40.0
2009	63.7	29.1	7.2	27.0	4.2	42.9
2010	63.8	30.7	5.5	25.1	3.5	45.5
2011	68.4	26.4	5.2	21.8	3.9	47.2
2012	69.8	25.1	5.1	24.5	4.7	46.4
2013	72.7	21.8	5.5	21.0	3.8	45.8
2014	77.0	17.5	5.4	19.8	3.9	46.5
2015	79.3	15.5	5.2	15.8	2.9	46.6
2016	70.8	24.9	4.3	14.4	2.8	45.3

BC mortality has a distinct declining trend. This became especially apparent since 2009, when it amounted to 2.2 per 100,000, vs. 1.2 per 100,000 in 2016. Early detection is one of the main indicators in oncology (Table 2).

The annual analytical reports of oncological dispensaries [6] show the growth of early BC detection, with a decline of BC detection at stage IV. The early detection at stages I-II was 56.0% in 2005 vs. 70/8% in 2016, and at stage IV - 6.7% vs. 4.3% in 2016. This indicator corresponds with the decline of mortality from BC.

However, some inconsistencies are apparent. First of all, in the cancer registry stages I and II are still registered as the early stages despite the known significant difference between them, especially from the point of BC survival. In addition, the approaches to therapy selection are

very different for non-muscle invasive cancer ("superficial surface carcinoma", stages Ta, Tis, T1) and muscle-invasive BC (T2-T4). This inherently affects the cancer prognosis. Still, the cancer registry data does not allow differentiating these two stages.

Now, the "one-year mortality" indicator. The table clearly shows its decline from 23.4% in 2007 to 14.4% in 2016. It is known that only the patients with stage IV cancer die during one year, and the ratio of one-year mortality to the late detection of the disease is calculated to assess the reliability of detection of advanced cancer. Ideally, this indicator should strive for unity. If so, then the late detection of the disease is reliable. According to the table, the annual mortality to the late detection was 3.9 in 2007 vs. 2.8 in 2016 what indicates an incorrect determination of the stage of the disease.

**Table 3** – Treatment coverage of newly registered patients with BC

Year	Number of patients who completed specialized treatment (%)	With use of treatment methods (%):					
		Only surgical treatment	Only radiation therapy	Only chemotherapy	Combined treatment	Complex treatment	Chemo-radiation
2005	54.2	50.2	5.7	10.9	26.6	6.6	
2006	60.0	47.1	6.7	10.9	7.5	24.0	3.9
2007	62.5	48.5	4.9	9.8	10.3	24.4	2.2
2008	58.8	54.9	8.1	7.5	4.0	22.8	2.6
2009	54.8	49.4	7.5	4.5	8.4	27.8	2.4
2010	60.7	49.1	4.9	3.1	8.3	32.9	1.7
2011	80.9	52.5	6.4	5.1	3.2	30.6	2.2
2012	84.0	53.8	5.4	5.9	4.9	27	2.9
2013	87.8	53.5	5.0	6.3	3.1	29.8	2.3
2014	86.3	48.5	3.0	8.9	4.7	29.6	5.4
2015	90.4	42.5	10.6	9.1	8.5	25.4	3.9
2016	92.0	50.2	3.0	6.0	2.8	36.9	1.2

The annual analytical reports of oncological dispensaries showed the nature of treatment received by patients with BC. The annual analytical reports and indicators of cancer service of the Republic of Kazakhstan were reviewed from 2005 to 2010 [3-6]. The treatment coverage was about 54.2-62.5%. The column showed the number of patients

who completed treatment in the reporting year in %. That is, a part of the patients has not completed treatment in the reporting year and was transferred to the following year. Some patients were not eligible for treatment due to concomitant diseases. Still, the figure remained stable from year to year and was low till 2011, when the cover-

age reached 80.9%. By 2015, the treatment coverage was already 90.4%.

According to the table, 76.4% to 90.3% of patients who completed treatment in the reporting year underwent surgery (the sum of methods “only surgical treatment” + “combined treatment” + “complex treatment”) although surgery was known to be the main method of BC treatment [7]. The other part of patients received either chemotherapy or radiotherapy, or a combination thereof.

That means, 10% to 23.5% of patients who completed specialized treatment did not receive surgery and remained without an adequate treatment.

7.0% to 23% of newly diagnosed patients received radiation therapy each year in the form of independent or combined treatment (chemo-radiation, combined therapy).

Table 4 presents relevant data on radiation therapy among patients with registered relapse or continued BC growth.

**Table 4** – Number of patients who received radiation therapy due to a relapse or continued BC growth

Assessment criterion	Year					
	2011	2012	2013	2014	2015	2016
Group of patients with BC	3298	3185	3266	3281	3402	3586
Number of patients received the radiation therapy, abs.	103	109	87	120	164	115

Again, the author was not able to find the information on how many patients from the total registered cohort belonged to the 3<sup>rd</sup> clinical group due to the relapses. It was known only that a fairly large number of patients with miBC underwent radiation therapy though radiation therapy was not radical in BC and was used as a part of multimodal therapy or as a palliative treatment to stop bleeding. The reason for frequent use of radiation therapy in miBC was mostly the refusal of patients to undergo organ-resecting surgery, or a concomitant pathology or age limitation for radical surgery. In that respect, the oncologists (oncurologists, surgeons, radiologists) could have a role to play. They were to know and inform the patients about relevant advantages and disadvantages of offered treatment. Moreover, most of these patients would suffer either from rapid cancer progression with distant metastases or would undergo organ-resecting surgery but in worse conditions.

The analytical reports provided an overall summary of treatment methods with no possibility to define which patients had a “superficial” cancer and which had a muscle-invasive cancer. Obviously, only radiotherapy, chemotherapy, chemo-radiation, complex treatment were referred to

patients with muscle-invasive cancer, whereas only surgical and combined treatment was partially associated with treatment of a “superficial surface” carcinoma, and partially – with the treatment of miBC. Therefore, the implementation of radical cystectomies has been reviewed by regions.

The table reflected data for all patients with BC, not only newly detected patients. According to Table 5, the number of radical cystectomies was growing. At the beginning of the century, this kind of surgery was performed only in Karaganda and Almaty oncological dispensaries. Early on, the ureter egestion to the skin or ureterosigmoidostomy was commonly used for urine derivation. Later on, the number of orthotopic bladder and urostomy has increased. I.e., 16 cystectomies, including 7 cutaneostomies, were performed in oncological dispensaries in 2005 vs. 99 radical cystectomies in 2016. Unfortunately, about j of these operations were palliative. The number of patients who actually needed that treatment could be much higher if the BC detection by regions was compared to the number of patients with miBC, taking into account the progression of nmiBC into miBC and the disease recurrence.

**Table 5** – The number of radical cystectomies performed in oncological dispensaries (OD)

Oncological dispensary	Number of radical cystectomies, n (of them, cutaneostomies)										
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Akmola Region	-	-	-	-	-	1	-	2	-	1	2
Almaty Region (Taldykorgan)	-	-	-	1 (1)	-	2 (2)	1 (1)	-	4 (1)	4 (2)	4 (1)
Almaty Regional OD	-	-	-	-	-	3 (2)	3 (1)	1	6 (2)	1	3
Atyrau Region	-	-	-	-	-	-	1	-	-	-	-
East Kazakhstan Region	-	-	-	-	-	-	5 (2)	9 (4)	6 (3)	12 (6)	9 (4)
Zhambyl Region	-	-	-	-	-	-	-	1	-	-	1
West Kazakhstan Region	-	-	-	-	-	-	-	1	3	3	4
Karaganda Region	7 (3)	9 (5)	16 (7)	16 (10)	14 (9)	18 (10)	15 (8)	17 (8)	14 (7)	19 (10)	15 (8)
Aktobe Region	-	-	-	-	-	-	-	1	-	3	1
Qyzylorda Region	-	-	-	-	-	1	3	2	2	1	3
Qostanay Region	-	-	-	-	-	-	-	10 (5)	8 (4)	8 (2)	8 (1)
Mangystau Region	-	-	4 (4)	2 (2)	2 (2)	-	-	-	-	-	-
Pavlodar Region	-	-	-	1	1	2	6 (1)	7	6 (2)	8	6
North Kazakhstan Region	-	13 (3)	6 (1)	4 (2)	13 (1)	5 (4)	6 (1)	7 (1)	5 (2)	3 (1)	8 (1)
South Kazakhstan Region	-	6 (4)	3 (1)	4 (1)	4 (3)	4 (2)	5 (3)	5 (3)	4 (1)	6 (1)	5 (2)
The city of Almaty	9 (4)	7 (3)	11 (5)	12 (3)	12 (6)	15 (3)	18 (3)	16 (4)	14 (5)	15 (4)	17 (5)
The city of Astana	-	-	-	3 (3)	3 (3)	4 (1)	9 (3)	8 (1)	10 (2)	10 (1)	13 (1)
Total	16 (7)	35 (15)	40 (18)	33 (22)	49 (24)	55 (24)	72 (23)	87 (26)	82 (29)	94 (27)	99 (23)

Radical surgery is performed in the Kazakh Institute of Oncology and Radiology (KazIOR) since early 2000s. The urine derivation has been mainly achieved by ureterocutaneostomy with dry or moist urostomy. The wider application of orthotopic bladders for urine diversion is done in KazIOR since 2006. This type of surgery is a high-tech medical care. As KazIOR provides postgraduate specialization, since 2009 we have trained 17 doctors of oncological dispensaries (urologists, surgeons). Besides, these technologies are annually transferred to the regions by providing master classes with international experts and visiting master classes to different dispensaries. As a result, these operations are now performed in most of the regions of the country. If earlier KazIOR has performed 50-60 operations a year, this number has halved since 2015 as these operations are now performed in the regions.

**Conclusion.** The following conclusions have been made after the study of the cancer registry and the annual analytical reports of oncological dispensaries. The doctors involved in diagnostics and treatment of cancer diseases in their everyday clinical practice should be guided by the "Periodic diagnostics and treatment protocols" and, first of all, they must be able to establish the disease stage correctly. nmIBC has a high rate of recurrence and often progresses into miBC. Muscle-invasive BC is an aggressive type of cancer. Surgery is the leading method of miBC treatment. Radical cystectomy ensures highest survival rate. However, the number of radical cystectomies remains low and insufficient for the radical treatment of that stage of disease. The share of both primary and follow-up patients who undergo radiotherapy is still high though it often leads to a non-radical treatment. In most cases, that is due to the refusal of patients and sometimes doctors to conduct organ-dissecting treatment which is caused by the lack of awareness. Taking the aforesaid into account, in one of the following publications we will present the comparative results of different treatment of patients with miBC in KazIOR.

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