



INFLUENCE OF CLINICAL PATHOLOGICAL CHARACTERISTICS OF ADENOCARCINOMA OF THE STOMACH ON SURVIVAL TIME OF PATIENTS POST-SURGERY

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ABSTRACT

Aim: The aim of this study was to determine the influence of specific prognostic factors on the survival time of patients who have been operated on in Tuzla Canton in Bosnia and Herzegovina.

Method: Retrospective - prospective five-year study that was performed in University Clinical Center in Tuzla, the Department of Surgery, included 100 patients treated from adenocarcinoma in the period 01.01.2010 - 31.12.2015. Data about type of gastric resection, lymphadenectomy and splenectomy, were obtained from operational note and formed a first group of prognostic factors. The second group included pathological characteristics of the tumor, including size, location, its histological type, Borrmann's classification, differentiation, characteristics of resection lines, number of metastatic lymph nodes, peritoneal dissemination, and distance metastases. Data obtained from the Institute of Pathology, University Clinical Center in Tuzla.

Results: Tumors located in the antrum ($p < 0.0446$) were the most valuable for prognoses. Subtotal gastrectomy had the best statistical value ($p < 0.036$). In 79% cases where splenectomy was not performed, the survival time was longer making splenectomy a significant prognostic factor ($p < 0.0013$).

Conclusion: Factors that influenced survival time, as a measure of relative risk, include tumor size, its location, the TNM stage, and the type of operation. A longer survival time 12 - 15 months was present where subtotal gastrectomy was performed without splenectomy on patients with a tumor in the antrum. With tumor < 5 cm, at stage T3 and T4, and where other types of operations were performed, the average survival time was 7 - 8 months.

KEY WORDS: adenocarcinoma of the stomach, prognostic factors, type of operation, survival time.

Introduction

Carcinoma of the stomach is the leading cause of death in the world, following lung cancer. (1,2) The high number of incidents of carcinoma of the stomach and the death rate associated with this cancer in the Tuzla Canton in Bosnia and Herzegovina motivated this research study. Histopathological classification is the most important classification system in prognoses of survival time for patients with carcinoma of the stomach, compared to other classification systems. (3,4) Surgery remains the most important treatment in treating adenocarcinoma of stomach. (5)

The evolution of surgical treatment of carcinoma of the stomach is related to five factors: the extent of gastritis resection needed for potential cure of the lesion, the role of per gastric lymphadenectomy, the importance of the oral and distal resection line, the role of splenectomy, and the effects on neighbouring organs. (6,7,8,9) Clinical pathological characteristics of tumor and lymph nodes are also important prognostic factors in determining survival time. (10,11)

This study analyzes the influence of specific prognostic factors on the survival time of patient post- surgery. The aim of this study was to determine the most important prognostic factors that were directly linked to the survival time of patients with carcinoma of the stomach post-surgery in Tuzla Canton in Bosnia and Herzegovina.

Patients and Methods

This retrospective-prospective study included one hundred patients treated for adenocarcinoma of stomach during a 5-year in the period from 01.01.2010 to 31.12.2015. Only patients with pathologically verified adenocarcinoma were included in the study. The type of surgery, lymphadenectomy and splenectomy, were examined as first group of prognostic factors. The second group included pathological characteristics of the tumor. Tumor characteristics and lymph nodes by TNM classification were obtained from Institute of Pathology, at the University Clinical Center in Tuzla. The type of gastric resection (R0 to R3) was obtained from the surgery findings, the Department of Surgery, University Clinical Center in Tuzla. Post-operative check-ups of patients were conducted after 3 months, 6 months, 2 years and 5 years. The data collected was based on information filled in on standard forms submitted to register malignancy with the Department of Health of Tuzla Canton.

Statistical analysis was completed using the statistical program SPSS, Version 17.0. The first step, the univariate analysis was done to determine how demographic and clinical variables influence the results of analysis. This analysis was based on Log-rank test. The second analysis was done according to Cox model and used good prognostic factors from univariate analysis. The difference in outcomes was considered to be significant when $p < 0.5$.

RESULTS

The average age of patients was 61 years (SD 11.28). The study included 66 male patients and 34 female patients. The ratio of male and female solos was 1.94 : 1. The age distribution is presented in Figure 1.

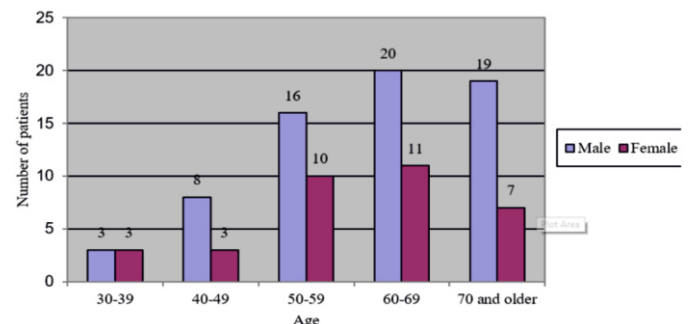


Figure 1. Patients' age and gender distribution

Characteristics of the tumor and its location in the stomach for the examined patients is shown in Table 1. The most occurring cases were of tumors with a size between 2 and 5 cm, located in the antrum, and with characteristic of ulcer.

Table 1. Characteristics of tumors in operated patients with gastric adenocarcinoma.

Variable	Subgroup	Frequency	
		n	%
Tumor size	up to 2 cm	28	28.00
	2-5 cm	45	45.00
	over 5 cm	27	27.00
Histological type	adenocarcinoma	71	71.00
	signet ring	27	27.00
	others	2	2.00
Tumor location	cardia	12	12.00
	corpus	36	36.00
	antrum	39	39.00
	pylorus	13	13.00
Borrmann classification	polyp (1)	11	11.00
	vegetation (2)	22	22.00
	ulcer (3 and 4)	67	67.00

Type of operations are presented in Table 2. 66 %, of patients had resection R1 and R2, and 41% of patients had total gastrectomy, 40% of patient had subtotal gastrectomy. Other types, such as Billroth II resection and palliative surgery were less common. A negative resection margin was present in 66% of cases. Peritoneal dissemination was not present in 80% of patients, and during operation, the splenectomy was not performed in 79% of cases.

Table 2. Factors related to surgery in patients with gastric adenocarcinoma.

Variable	Subgroup	Frequency	
		n	%
Degree of resection	R0	34	34.00
Total gastrectomy	R1 and R2	66	66.00
		41	41.00
		40	40.00
		13	13.00
		4	4.00
Subtotal gastrectomy		2	2.00
Billroth II			
Palliative surgery			
Inoperable			
Resection lines	negative	66	66.00
	proximal positive	10	10.00
	distal positive	22	22.00
	both positive	2	2.00
Peritoneal dissemination	present	20	20.00
	absent	80	80.00
Splenectomy	performed	21	21.00
	not performed	79	79.00

Histopathological stages of the tumor and characteristics of metastasis of lymph nodes are presented in Table 3. Positive lymph nodes were present in 62% of patients post-surgery with 32% of patients with N1 distant metastasis. TNM T4 advanced stage was present in 45% of cases while 55% of patients had a G III poorly differentiated tumor.

Table 3. Stage of tumors in patients with gastric adenocarcinoma

Variable	Subgroup	Frequency	
		n	%
Positive lymph nodes	Yes	62	62.00
	No	38	38.00
Metastases in lymph nodes *	N1	32	32.00
	N2	24	24.00
	N3	6	6.00
Distant metastases	absent	76	76.00
	liver	10	10.00
	pancreas	5	5.00
	lungs	4	4.00
	others	5	5.00
TNM stage**	T1	1	1.00
	T2	23	23.00
	T3	31	31.00
	T4	45	45.00
Histopathological stage ***	I	1	1.00
	II	44	44.00
	III	55	55.00

* N1 metastasis in 1-6 lymph nodes, N2-in 7-15, N3 in more than 15 lymph nodes;

** The stage of the International Union Against Cancer (UICC) TNM classification;

*** I, II and III are G1 well differentiated, G2 moderately differentiated, G3 poorly differentiated tumor respectively according to UICC;

The univariate analysis of tumor characteristics and the average survival length is presented in Table 4. The variables that showed significance in survival prognoses are tumor size ($p=0.0439$) and location ($p=0.0446$). TNM stage of adenocarcinoma was also significant ($p=0.0323$) and study showed that T1 and T2 stages resulted in longer survival time. Other variable did not show statistical value.

Table 4. Univariate analysis of the relation between tumor characteristics and average survival time

Variable	Subgroup	Average survival time (months)	p*
Tumor size	up to 2 cm	11.0	0.0439
	2-5 cm	9.5	
	over 5 cm	7.0	
Histological type of tumor	adenocarcinoma	9.0	0.0580
	signet ring	9.0	
	Other	4.0	
Tumor location	cardia	9.0	0.0446
	corpus	8.0	
	antrum	15.0	
	pylorus	8.0	
Bormann classification	polyp (1)	9.0	0.2078
	vegetation (2)	7.0	
	ulcer (3 and 4)	9.0	
Positive lymph nodes	Yes	9.0	0.6671
	No	9.0	
Metastasis in lymph nodes	N1	9.0	0.4654
	N2	9.0	
	N3	4.0	
Distant metastasis	present	7.5	0.1337
	absent	9.5	
TNM stage***	1 and 2	19.0	0.0323
	3 and 4	8.0	
Histopathological stage	I and II	9.0	0.6279
	III	7.0	

* Value determined by Log-rank test

** N1: metastasis in 1-6 lymph nodes, N2: 7-15, N3: more than 15 lymph nodes

*** Stage according to International Union Against Cancer (UICC) TNM classification

Where subtotal gastrectomy was performed, the average survival time post-surgery was 13 months ($p<0.0036$). The resection R0 showed a better average survival time (12 months), compared to R1 and R2 ($p<0.0029$). Furthermore, where splenectomy was not performed ($p<0.0013$), patients were found to have a longer average survival time (12 months). (Table 5).

Table 5. Univariate analysis of the relation between type of operation and the survival time post-surgery

Variable	Subgroup	Average survival time (months)	p*
Type of operation	Total gastrectomy	9.0	0.0036
	Subtotal gastrectomy	13.0	
	Palliative	3.0	
Degree of resection	R0	12.0	0.0029
	R1 and R2	8.0	
Peritoneal dissemination	present	7.0	0.1885
	absent	9.0	
Splenectomy	performed	6.0	0.0013
	not performed	12.0	

* Value determined by Log-rank test;

Characteristics of the tumor and the type of operation performed are statistically important for estimating the survival time, and were analyzed using the Cox method of relative risk. Table 6 includes the results of the Cox model. The variables include the occurrence of tumors larger than 5 cm, the location of tumor on pylorus, the type of operation performed (total gastrectomy, palliative operation, partial resection, splenectomy) and the TNM stages T1 and T2. Multivariable analysis of prognostic factors that had statistical value provided the measures of relative risks, Hazard Ratio (HR).

Table 6. Multivariable analysis as per Cox model

Variable	b	P	HR*	95% CI
Tumor size (over 5 cm)	0.5288	0.06443	1.6969	0.9716 – 2.9636
Location of tumor on pylorus	0.5974	0.09475	1.8174	0.9050 – 3.6494
Total gastrectomy	0.08055	0.7589	1.0839	0.6497 – 1.8082
Palliative operation	1.2710	0.2668	3.5643	0.3826 – 33.2073
Partial resection	0.5059	0.03625	1.6584	1.0354 – 2.6563
Splenectomy	0.3235	0.2866	1.3819	0.7646 – 2.4977
TNM T1 and T2	-0.3654	0.1760	0.6939	0.4099 – 1.1748

*HR (Hazard ratio) – measure of relative risk

DISCUSSION

Surgery remains the most important method for treating adenocarcinoma of stomach. The influence of specific prognostic factors in our study showed results that are similar to those of other authors. (4,10,12)

The survival time decreases when the tumor size is larger than 5 cm. Subtotal gastrectomy, compared with total gastrectomy, resulted in a better survival time. Of all patients, 39% had a tumor located in the antrum. The average length of their survival time was the longest, up to 15 months, compared to cases in which tumors were located in the corpus, pylorus or cardia. The univariate analysis by Yokota and her associates showed 94.3% survival time when the tumor was < 2 cm, and 26.3% for tumors sized 2-7 cm. (13). In our study, 28% patients had tumors < 2 cm and their average survival time was 11 months. Furthermore, 27% of patients had tumors > 5 cm and their average length of survival was 7 months. The most occurring were T3 and T4 stage tumors. For these patients, the average survival time was 9 months. The analysis of serious invasion of the tumor gave the same results as the studies of other authors Oh CA, Kim and Hanson. (14,15,16)

In relation to TNM stages, the average survival time post-surgery was 9 months for T1 stage in 1% of patients, 7 months for T2 stage in 23% of patients, 9 months for T3 stage in 31% of patients, and 9 months for T4 in 45 % of patients.

Distant metastasis was not present in 76% of patients. Metastasis in the liver, pancreas, and lungs was present in 10%, 5% and 4% of patients, respectively. In relation to the type of operation and without distant metastasis, the average survival time was 9.5 months. Peritoneal dissemination was not present in 80% of cases and impacted the survival time, as well as the resectability of adenocarcinoma of the stomach. The cases with peritoneal dissemination amounted to 20% and their average survival time was 7 months. (15,17)

Similar to the findings of our study, the univariate analyses of other researchers showed a good prognosis for T1 tumors. (11,16) Studies of Dutch authors that included 473 patients was also completed according to TNM classification. (4,18) Our study showed an average survival time 9 months.

A histopathological G3 stage with a bad differentiated tumor was the most common case, with an occurrence of 55%, compared to G2 and G1 stages, which matches the prognostic studies of other authors. (12)

R0 resection, which was statistically significant ($p < 0.0029$), resulted in an average survival time of 12 months and was performed on 34% patients. R1 and R2 resections resulted in 8 months of average survival time and were performed on 66% patients. R0 resection with extended lymphadenectomy was included in studies of Markar, Dikken and Ruize as well. (2,18,19)

The type of surgery was a statistically important factor ($p < 0.0036$) for the prognosis of post-surgery survival time in patients. Subtotal gastrectomy was performed on 40% patients and their average survival time was 13 months. The patients with total gastrectomy formed 41% and average survival time 9 months. Other types surgeries such as Billroth II resection and palliative surgery had average survival time of 3 months.

The analysis of prognostic factors related to the resection type confirms that subtotal gastrectomy, compared to other operation types, was the best method. (17,18,20)

Our pathological analysis of resection lines gave the following results: 66% of patients had negative resection lines, 22% had distal positive lines, 10% had proximal positive lines, and 2% patients had both positive resection lines.

Splenectomy was not performed on in 79% patients. This was a statistically significant factor ($p < 0.0013$) and resulted in an average survival time of 28 months. Lorenzo found the same results. (21)

Multivariable analyses of prognostic factors that were taken as measures of relative risk, were completed by the Cox method. The results were the same as those in other studies. (12,19,22)

Our study shows that patients with tumor sizes < 2 cm located in the antrum and with T1 and T2 stages per TNM classification, had longer survival times. Patients with subtotal resection and patients who did not have splenectomy performed on them, also had longer survival times.

CONCLUSION

The analysis of prognostic factors determined the measures of relative survival time risks for patients, who had underwent surgery of gastric adenocarcinoma. Patients with a tumor larger than 5 cm, at T3 and T4 stages, had a bad prognosis. Patients' average survival times were between 7 and 8 months, respectively. Patients with a tumor in the antrum had 15 months average survival time. Where subtotal gastrectomy was performed, the average survival time was also 13 months. R0 resection resulted in an average of 12 months survival time. In cases when splenectomy was not performed, average survival time was 28 months.

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