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Research Article

Features of Histological Forms of Tumor Growth in Patients Who Underwent Combined Surgery for Stomach Cancer

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Abstract
The morphological type of tumor is a crucial factor in selecting the type and volume of surgery.
The objective of the research was to determine the effect of tumor histological type on survival rates in patients with locally advanced stomach cancer after combined surgery.
Materials and methods. The study included 990 patients; there were 714 men and 276 women. All patients underwent combined surgery: distal subtotal gastric resection was performed in 222 cases; proximal subtotal gastric resection was used in 129 cases; gastrectomy was applied in 639 cases. Statistical analysis of the obtained data was performed using the SPSS 13.0 software program. The results were considered statistically significant at $p<0.05$.
Results. The study of certain morphological types of tumor depending on the patients' age and sex, as well as clinical and morphological features revealed a significant predominance of adenocarcinoma (77.1%) over other types and a significantly smaller number of undifferentiated tumors – 20.6%; squamous cell cancer and small-cell cancer constituted 1.3% and 1.0%, respectively. The average life expectancy after surgery was 37.51 ± 2.69 months (p=0.021); in women, it was slightly higher compared to men – 43.75 ± 5.70 months vs. 35.13 ± 3.02 months (p=0.057). The overall 5-year survival rate for all patients was 17.32 ± 1.49%; for men – 16.11 ± 1.72% (p=0.005), for women – 20.46 ± 2.99% (p=0.399); however, these differences were not statistically significant (p=0.087).
Conclusions. After surgery, there were no significant differences in the average life expectancy of patients with the same histological forms of gastric adenocarcinoma between men and women ($p>0.05$), while significant differences were observed between patients (both men and women) with adenocarcinoma and undifferentiated adenogenic stomach cancer ($p<0.05$).

Keywords
stomach cancer; histological forms; combined surgery

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Problem statement and analysis of the recent research

Despite advances in early cancer detection, stomach cancer (SC) remains the leading cause of cancer death after lung cancer worldwide [4]. It is mainly due to the fact that a significant proportion of locally advanced forms of SC is diagnosed too late, especially in Ukraine (over 20-25%) [1].

Surgery which involves achieving a R0 resection, is often used in patients with locally advanced forms (T4) of SC [8]. Over recent years, the increase in the rate of complications in the postoperative period as well as survival rate has been actively discussed. Some researchers have reported minor changes in the survival of patients who underwent combined surgery [6]. However, significantly higher rates of complications and mortality as well as a slightly longer duration of in-patient treatment due to extended resections have been indicated by other authors [6].

The microscopic type of tumor is a crucial factor in selecting the type and volume of surgery [7]. In addition, other clinical and pathological characteristics of tumor such as the depth of invasion, lymph node status, macroscopic type, tumor size and others affect the prognosis of locally advanced SC.

The objective of the research was to study the effect of histological type of tumor on survival and prognosis of patients with locally advanced SC after combined surgery.

1. Materials and methods

The study included 990 patients; there were 714 men and 276 women. All patients underwent various types of combined surgery for SC in Lviv Regional Clinical Oncology Center. Surgery was considered "combined" when the main type of surgery (subtotal gastric resection or gastrectomy) was combined with en bloc resection or removal of other (related) organs (the mesentery of the transverse colon, the transverse colon, the body and tail of the pancreas, spleen, diaphragm, soft tissue of the anterior abdominal wall). Distal subtotal gastric resection (n=222), proximal subtotal gastric resection

(n=129) or gastrectomy (n=639) were performed depending on the location of the primary lesion and other JGCA criteria [5]. The additional organ resection was performed to achieve R0 resection; in some cases, due to iatrogenic damage to the organ. All the data were statistically processed using the SPSS 13.0 software program (Chicago, IL). The obtained numerical indicators were presented as M±m, and the difference between groups was compared using the independent bilateral T-test. To compare frequency parameters between groups, the χ^2-square test (Fisher's exact test) was used. The time interval between the time of surgery and the date of death or last contact (if alive) was used to analyze survival data by means of the Kaplan-Meier method and the log-rank test. In all cases, the results were considered statistically significant at $p<0.05$

2. Results

The average age of patients was 60.02±0.30 years (generally from 21 up to 87 years); male patients prevailed over female patients– men:women = 2.6:1.0 (72.1%: 27.9%). Among all combined surgical procedures, combined gastrectomy predominated over combined subtotal gastric resection and proximal gastric resection - 5:2.9:1.

The average life expectancy of 701 (512 men, 189 women) patients after surgery was 37.51±2.69 months (p=0.021); in women, it was slightly higher compared to men – 43.75±5.70 months vs. 35.13±3.02 months (p=0.057). The median survival time was 12.03±0.59 months, 20.46±2.99 months and 16.11±1.72 months, respectively (Table 1). The highest average life expectancy was in patients with adenocarcinoma – 41.21±3.29 months; the lowest average life expectancy was in patients with squamous cell cancer – 10.79±4.73 months (p=0.041); significantly lower average life expectancy was observed in patients with undifferentiated cancer – 25.29±3.28 months (p=0.015). The study of certain morphological types of tumors depending on the patients' age and sex, as well as clinical and morphological features revealed a significant predominance of adenocarcinoma (77.1%) over other types and a significantly smaller number of undifferentiated tumors – 20.6%; squamous cell cancer and small-cell cancer constituted 1.3% and 1.0%, respectively (Table 2).

3. Discussion

There were some differences in the average life expectancy by neoplasm morphology; the highest average life expectancy was observed in patients with adenocarcinoma of the stomach – 41.213±3.291 months, and the lowest one was observed in patients with squamous cell cancer – 10.793±4.734 months. There were detected significant differences in life expectancy between these groups of patients (p=0.041) and patients with adenocarcinoma as well as undifferentiated cancer (25.298±3.281 months) – p=0.015. There were no significant sex differences within the same type of morphology ($p>0.05$) [3]. The differences between life expectancy of patients with adenocarcinoma and small-cell cancer (29.34±28.97 months) were insignificant– p=0.491. In both male and female patients, the same patterns were mostly observed; it was apparently due to small number of observations – the differences were not determined between patients with small-cell cancer and squamous cell cancer; however, there was a significant difference between patients with adenocarcinoma and undifferentiated cancer (p=0.011). It should be noted that within each individual morphological form, there were observed minor gender differences; however, all of them were not statistically significant ($p>0.05$) [6, 8, 9]. There were determined no statistically significant differences in the average age of patients with different morphological types ($p>0.1$) [2]. Despite the overwhelming number of male patients ($p<0.01$), the most significant differences in adenocarcinomas and undifferentiated cancer were identified in both men and women ($p<0.01$) (Table 2), in rest cases there were not significant differences between the proportions of men and women ($p>0.05$) [6]. The most marked differences in the relative number of exophytic and endophytic tumors were found between adenocarcinoma and undifferentiated cancer ($p<0.01$) as well as endophytic tumors – between adenocarcinoma and small-cell cancer ($p<0.05$). There was no significant difference in the number of exophytic and endophytic tumors between the macroscopic forms of adenocarcinoma ($p>0.1$); however, the number of mesophytic tumors was significantly smaller compared to the previous one ($p<0.01$). Such value was not typical for other morphological types of tumors; however, undifferentiated tumors had significantly more endophytic forms ($p<0.01$) [8]. The predominant depth of invasion was T4 ($p<0.01$).

The status of affected lymph nodes in patients with adenocarcinoma corresponded with category N0 and N1 ($p<0.01$); similar tendency was typical for patients with undifferentiated cancer ($p<0.01$); for other morphological types these ratios were not significant ($p >0.05$) [6, 8].

In patients with adenocarcinoma, combined gastrectomy predominated over combined subtotal and proximal resection 4:2.5:1 ($p<0.01$); the same tendency was determined for other morphological types; the most expressed tendency was observed in patients with undifferentiated cancer – 6:5:1 [10].

The overall 5-year survival rate for all patients was 17.32± 1.49%; for men – 16.11±1.72% (p=0.005), for women – 20.46±2.99% (p=0.399) (Table 1, Fig. 1); however, these differences were not statistically significant (p=0.087). As for the difference in the 5-year survival rate by morphology, the difference was significant between male patients with adenocarcinoma and undifferentiated cancer (17.52±2.05% and 12.53±3.27%, respectively p=0.041 [3]; in other cases, the 5-year survival was not achieved (Table 1, Fig. 2). In female patients, the highest 5-year survival was observed in patents with adenocarcinoma 24.69±3.96% (Table 1, Fig. 3), in patients with undifferentiated cancer – 11.47±4.06, there was no significant difference between them (p=0.502); in other cases, the 5-year survival rate was not reached.

Table 1. Average life expectancy of patients with stomach cancer depending on histological forms of tumor growth and gender

#	Histological forms (WHO)	Average life expectancy (months) M	±m	95% confidence interval Lower limit	Upper limit	Median of average life expectancy (months) M	±m	5-year survival rate (%) M	±m
				All patients					
1	Adenocarcinoma	41.21	3.29	34.76	47.66	12.85	0.88	19.33	1.83
2	Small-cell cancer	29.34	28.97	0.00	86.13	0.39	0.05	33.33	27.22
3	Undifferentiated cancer	25.29	3.28	18.87	31.73	9.73	1.26	12.04	2.55
4	Squamous cell cancer	10.79	4.73	1.51	20.07	5.29	1.74	-	-
	Total	37.51	2.69	32.24	42.78	12.03	0.69	17.32	1.49
				Men					
5	Adenocarcinoma	37.99	3.59	30.95	45.04	12.03	0.84	17.52	2.05
6	Small-cell cancer	0.36	0.03	0.29	0.43	0.33	-	-	-
7	Undifferentiated cancer	24.74	4.03	16.85	32.62	8.45	0.98	12.53	3.27
8	Squamous cell cancer	6.57	2.48	1.72	11.42	5.29	2.37	-	-
	Total	35.13	3.02	29.21	41.05	11.28	0.77	16.113	1.72
				Women					
9	Adenocarcinoma	50.45	7.48	35.786	65.11	14.69	1.76	24.69	3.96
10	Small-cell cancer	87.29	0.00	87.29	87.29	87.29	-	1.00	0.01
11	Undifferentiated cancer	26.33	5.46	15.62	37.04	12.13	1.66	11.47	4.06
12	Squamous cell cancer	40.34	0.00	40.34	40.34	40.34	-	-	-
	Total	43.75	5.70	32.58	54.93	14.17	1.43	20.46	2.99

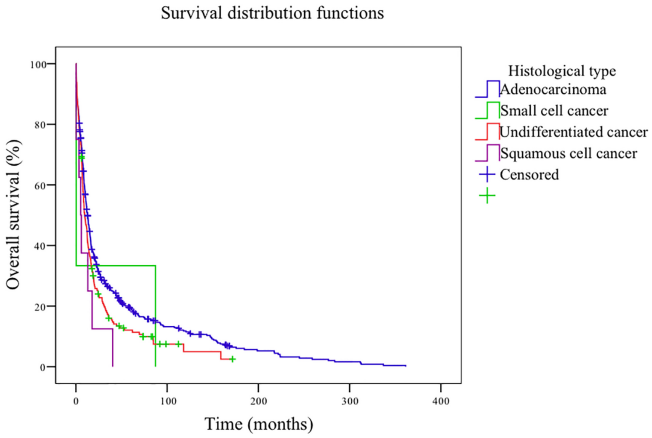

Figure 1. Comparison of the distribution functions of survival by the histological type in patients who underwent combined surgery.

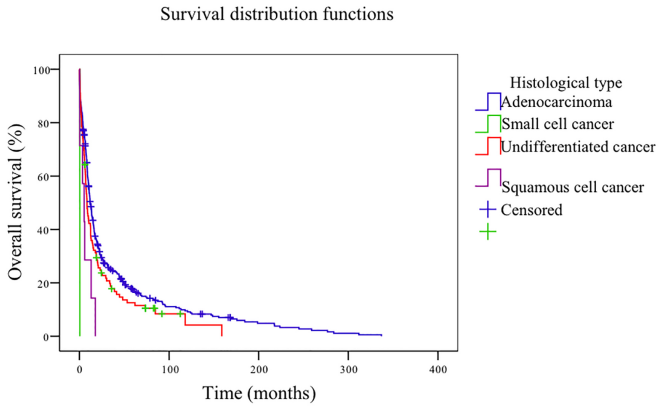

Figure 2. Comparison of the distribution functions of survival by the histological type in male patients who underwent combined surgery.

Table 2. Clinical and morphological data of patients with different histological types of stomach cancer

	Adenocarcinoma1 (n=763)	Small-cell cancer2 (n=10)	Undifferentiated cancer3 (n=204)	Squamous cell cancer4 (n=13)	p-value
Age, years	60.58±0.34	55.20±2.12	58.84±0.92	59.00±3.01	p^{1-2}=0.793 p^{1-3}=0.363 p^{1-4}=0.653
Sex					
Women	197 (25.8%)	4 (40.0%)	74 (36.3%)	1 (7.7%)	p^{1-2}>0.05 p^{1-3}<0.01 p^{1-4}>0.05
Men	566 (74.2%)	6 (60.0%)	130 (63.7%)	12 (92.3%)	p^{1-2}>0.05 p^{1-3}<0.01 p^{1-4}>0.05
Macroscopic type					
Exophytic	272 (35.6%)	2(20.0%)	28 (13.7%)	5 (38.5%)	p^{1-2}>0.05 p^{1-3}<0.01 p^{1-4}>0.05
Endophytic	224 (29.4%)	8 (80.0%)	90 (44.1%)	3 (23.1%)	p^{1-2} <0.05 p^{1-3}<0.01 p^{1-4}>0.05
Mesophytic	132 (17.3%)	-	32 (15.7%)	3 (23.1%)	p^{1-3}>0.05 p^{1-4}>0.05
Cancer originating from gastric ulcer	9 (1.2%)	-	1 (0.5%)	-	-
Tumor localization					
Proximal	381 (49.9%)	3 (30.0%)	73 (35.8%)	12 (92.3%)	p^{1-2}>0.05 p^{1-3}<0.01 p^{1-4}<0.01
Body	147 (19.3%)	1 (10.0%)	69 (33.8%)	1 (7.7%)	p^{1-2}>0.05 p^{1-3}<0.01 p^{1-4}>0.05
Distal	185 (24.2%)	4 (40.0%)	33 (16.2%)	-	p^{1-2}>0.05 p^{1-3}<0.05
Subtotal and total involvement	47 (6.2%)	2 (20.05)	28 (13.7%)	-	p^{1-2}>0.05 p^{1-3}<0.01
Multiple involvement	3 (0.3%)	-	1 (0.5%)	-	
Depth of invasion					
T1	10 (1.3%)	-			
T2	35 (4.6%)	-	14 (6.9%)	1 (7.7%)	p^{1-3}>0.05 p^{1-4}>0.05
T3	292 (38.3%)	1 (10.0%)	90 (44.1%)	7 (53.8%)	p^{1-2}>0.05 p^{1-3}>0.05 p^{1-4}>0.05
T4	415 (54.4%)	9 (90.0%)	100 (49.0%)	5 (38.5%)	p^{1-2}>0.05 p^{1-3}>0.05 p^{1-4}>0.05
Regional lymph nodes					
N0	314 (41.2%)	5 (50.0%)	67 (32.8%)	3 (23.1%)	p^{1-2}>0.05 p^{1-3}<0.05 p^{1-4}>0.05
N1	301 (39.4%)	2 (20.0%)	92 (45.1%)	7 (53.8%)	p^{1-2}>0.05 p^{1-3}<0.05 p^{1-4}>0.05
N2	97 (10.1%)	2 (20.0%)	36 (17.6%)	3 (23.1%)	p^{1-2}>0.05 p^{1-3}>0.05 p^{1-4}>0.05
N3	3 (0.4%)	-	3 (1.5%)	-	
Type of surgery					
Gastrectomy	463 (60.7%)	6 (60.0%)	161 (78.9%)	9 (69.2%)	p^{1-2}>0.05 p^{1-3} <0.01 p^{1-4}>0.05
Distal subtotal gastric resection	185 (24.2%)	4 (40.0%)	33 (16.2%)	-	p^{1-2}>0.05 p^{1-3} <0.05
Proximal subtotal gastric resection	115 (15.1%)	-	10 (4.9%)	4 (30.8%)	p^{1-3} <0.01 p^{1-4}>0.05

4. Conclusions

After surgery, there were no significant differences in the average life expectancy of patients with the same histological forms of SC between men and women ($p>0.05$), while significant differences were observed between patients (both men and women) with adenocarcinoma and undifferentiated adenogenic stomach cancer ($p<0.05$).

Taking into account the fact that combined surgery for SC is used mainly in older male patients, it should be considered in view of the current trend to the increase in the volume of surgery as well as the expansion of the indications for its performance.

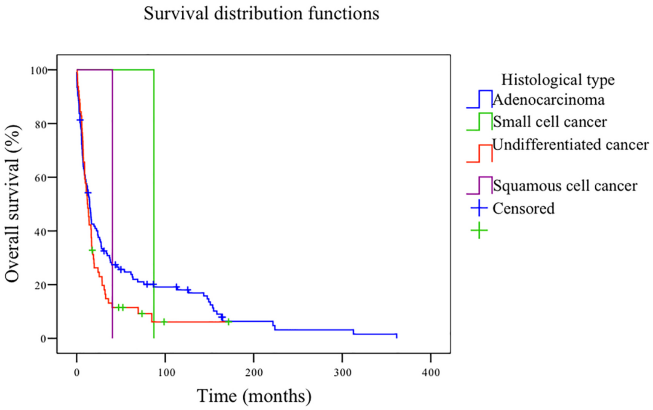

Figure 3. Comparison of the distribution function of survival by the histological type in female patients who underwent combined surgery.

5. Prospects for further research

Further researche should be directed to ascertain the survival of patients with locally advanced SC depending on the HER2 receptor expression of primary tumors.

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