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Survival analysis on data of different surgery techniques to evaluate risk of postoperative complications

Keywords

colectomy, censored medical survival data, comparison of surgery techniques

Abstract

Medical survival censored data of about 850 patients are evaluated to compare two basic surgery techniques. Data comes from patients who underwent colectomy in the University Hospital of Ostrava. The data has been screened into three general groups: all patients (data from both rectum and colon operations), data from rectum operations, data from colon operations. Two basic surgery techniques are used for the colectomy: either classical (open) or laparoscopic operation. Basic question which arises at the colectomy operation is which type of operation to choose to guarantee longer overall survival time. Two methodological approaches have been used to answer this relevant question. First is the non-parametric approach which results from Kaplan-Meier estimates of the survival function. For each data group two survival curves are constructed, i.e. for both open and laparoscopic type of operation. Final survival curves are compared and evaluated using advanced methods of statistical inference (e.g. log-rank test). Second is parametric approach which results from modelling of survival time. It is based on Maximum Likelihood Estimation method to estimate parameters of probability distribution of overall survival time. Moreover, two Weibull models are used to compare the two surgery techniques. Mean survival times assigned to particular types of operation are compared.

1. Introduction

1.1. Laparoscopic technique as a new trend in surgery of rectum and colon

The beginning of the 1990s is characterized by penetrative ingoing of minimally invasive techniques in surgery. These changes more or less affected all branches of surgery and partly or even totally replaced classical „open“ techniques in some cases. The colorectal surgery, which this paper is engaged in, is not an exception.

Minimally invasive surgery is generally associated with lower operative stress and more favorable post-operative course. On the other hand there are many negative factors in using laparoscopic techniques in colorectal surgery, which can participate in morbidity in large measure (e.g. the risk of capnoperitoneum, longer operative time and extreme positioning of patients). The comparison of morbidity and mortality after both types of surgeries is frequently published result of numerous medical investigations. For example, the consensus of European association of endoscopic surgery for colon carcinoma mentions, that there is no difference between morbidity of laparoscopic and open operations of colon, see [14].

Concerning the laparoscopic colectomy for cancer, a lot of information is now available resulting from numerous clinical analyses [1]-[2], [5], [7], [9], [13]. A lot of significant findings and observations have been accumulated to accept and proof merits of the laparoscopic surgery, as is for example better post-

operative course of treatment. Laparoscopic colectomy for cancer is minimally equivalent alternative to open operation in the treatment of cancer of colon.
Concerning the cancer of rectum cancer much less information is available. Meta-analyses comparing laparoscopic versus open surgery for rectal cancer are very rare and in fact they are mostly connected with short term results. Laparoscopic surgery for rectal cancer is still open problem in recent time and especially analysis of long term outcomes are eagerly awaited.

2. Non-parametric approach

2.1. Life distribution, basic relations

If failure (lifetime or survival time in medical applications [3]) distribution function F has a density f, the failure rate function (hazard function) $\lambda(t)$ is defined for those values of t for which $F(t) < 1$ by:

$$\lambda(t) = \frac{f(t)}{1-F(t)} = \frac{f(t)}{R(t)}, \tag{1}$$

where $R(t) = 1 - F(t)$ is survival function.

Knowing failure rate $\lambda(t)$, the survival function $R(t)$ can be easy derived as:

$$R(t) = \exp\left[-\int_0^t \lambda(x)dx\right] \tag{2}$$

and, knowing survival function $R(t)$, the mean survival time *MST* (or mean life) and standard error *SE* of the survival time can be derived as follows:

$$MST = \int_0^\infty R(x)dx \tag{3}$$

$$SE = \sqrt{2\int_0^\infty xR(x)dx - (MST)^2} \tag{4}$$

2.2. Kaplan-Meier estimator of survival function

Long-term survival analysis has been performed by the use of Kaplan-Meier method [4], [6].
Let us suppose randomly censored survival data. The result of our experiment can be as follows:

$$(W_1, I_1), \quad ..., \quad (W_n, I_n)$$

where W_j is either a time of death or a time in which the observation of *j-th* patient is stopped (withdrawn) and $I_j = 1$ resp. $I_j = 0$ (indicator) accordingly to the death resp. stopping time has occurred first.
Let us suppose that in the sample $W_1, \ldots, W_n$ no conformity has occurred. We create ordered sample $W_{(1)} < \ldots < W_{(n)}$. Let $I_{(j)}$ is indicator corresponding to $W_{(j)}$, $j = 1, \ldots, n$.

Notation: n_i … number of patients observed until $W_{(i)}$ (the time $W_{(i)}$ is not included). Then the Kaplan-Meier estimator of survival function $R(t)$ is:

$$\hat{R}(t) = \prod_{i:W_{(i)}<t} \left(1 - \frac{1}{n_i}\right)^{I_{(i)}} = \prod_{i:W_{(i)}<t} \left(\frac{n-i}{n-i+1}\right)^{I_{(i)}} \quad t \le W_{(n)}$$

$$\hat{R}(t) = 0 \qquad t > W_{(n)}. \tag{5}$$

It has an asymptotic normal distribution. Asymptotic variance for the estimator is known as Greenwood's formula [8]:

$$Var\,\hat{R}(t) = \hat{R}^2(t) \sum_{i:W_{(i)}<t} \frac{I_{(i)}}{(n-i)(n-i+1)} \tag{6}$$

$$t \le W_{(n)}.$$

2.3. Log-rank test

Often it is of interest to determine whether two subgroups of samples could arise from identical survival functions. First step we can do to solve this task is graphical display of the Kaplan-Meier estimator of the survival function for each of the groups. Generally we can say that if one survival function lies completely above another, than the proportion of subject estimated to be alive at any point of time for this group is greater than for the other group represented by the lower survival function. The main question is whether the difference between observed proportions is statistically significant.
We need test statistics that attempt to summarize differences between survival function estimators over the whole of the study period. The most commonly used statistics of this type can be viewed as censored data generalizations of such familiar rank tests as the Wilcoxon test and the Savage (exponential scores) test [12]. In this paper, only a heuristic construction of the generalized log-rank test is given [8].
This test is particularly good when the ratio of hazard functions in the populations being compared is approximately constant. It is constructed by calculating the number at risk and the number of observed deaths in one of the groups at each

observed survival time $W_{(i)}$, assuming that the survival function is the same in each of the two groups (we mark the groups as Group 0 and Group 1). This yields the estimator of expected number of deaths at time $W_{(i)}$ (for example using Group 1):

$$\hat{e} = \frac{n_{1i} d_i}{n_i} \tag{7}$$

and estimator of variance of d_{1i}, with hypergeometric distribution:

$$\hat{v}_{1i} = \frac{n_{1i} n_{0i} d_i (n_i - d_i)}{n_i^2 (n_i - 1)}. \tag{8}$$

The log-rank test statistics is defined as follows:

$$Q = \frac{\left[\sum_{i=1}^{m} (d_{1i} - \hat{e}_{1i}) \right]^2}{\sum_{i=1}^{m} \hat{v}_{1i}} \tag{9}$$

Notation:
n_{0i}, n_{1i} … number of study subjects at risk at observed survival time $W_{(i)}$ in Group 0 and Group 1 respectively
d_{0i}, d_{1i} … number of observed deaths in each group respectively
n_i … total number of study subjects at risk
d_i … total number of observed deaths

Under the null hypothesis that two survival function are the same, the p-value for Q may be obtained by the using of the chi-square distribution with one degree of freedom ($p = \Pr(\chi^2(1) \geq Q)$), if we assume that censoring experience is independent of the group, and that the total number of observed events and the sum of the expected number of events is large.

2.4. Results with data

2.4.1. Data from rectum operations

Data from rectum operations (so called diagnosis C20) have been used to construct Kaplan-Meier estimator of survival functions $R(t)$ according to formula (5), see *Figure 1*, including 95% confidence limits. All numerical values are expressed in months.

Table 1. Kaplan-Meier Estimates: rectum data

Operation technique	MST	SE
Laparoscopic	55.682	3.783
Open	56.032	3.875

In *Figure 2*, different curves are assigned to different operation techniques.

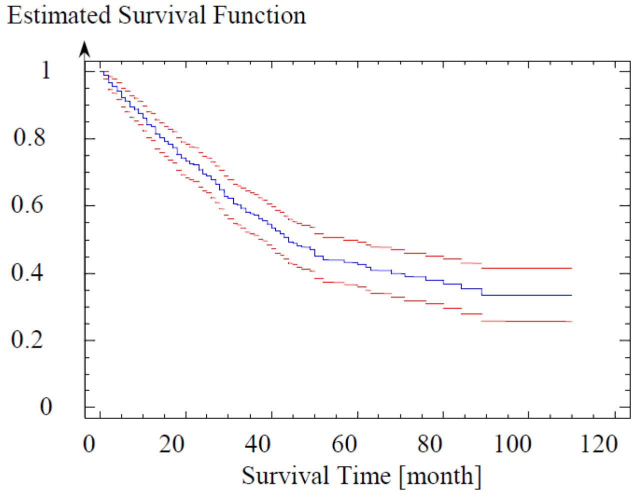

Figure 1. 95% confidence limits for survival function- surgery of rectum, all patients.

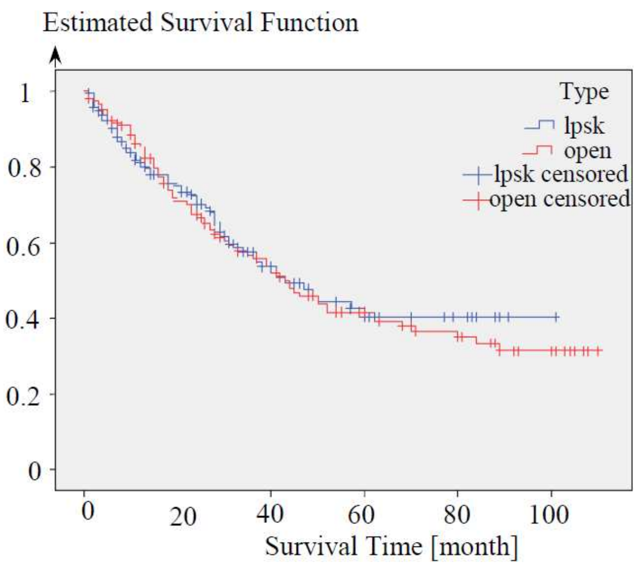

Figure 2. Survival function for surgery of rectum.

Table 2. Comparison of groups

Group	Total	Dead	Withdrawn	Withdrawn [%]
Lapar	191	72	119	62.30
Open	141	76	65	46.10
Total	332	148	184	55.42

Table 2 displays information regarding each group of data values. It shows the total number of patients under treatment tabulated, the number of patients which dead, the number of withdrawn or censored patients, and the proportion of censored patients. The log-rank test has also been performed to determine whether there is a statistically significant difference between the survival probabilities of the 2 groups of patients (χ^2 = 0.077, p-value = 0.781).

Since the *p*-value is great (still greater than 0.10), there is not a statistically significant difference between observed groups.

2.4.2. Data from colon operations

Data from colon operations have been used to construct Kaplan-Meier estimator of survival functions $R(t)$ according to formula (5), see *Figure 3*, including 95% confidence limits.

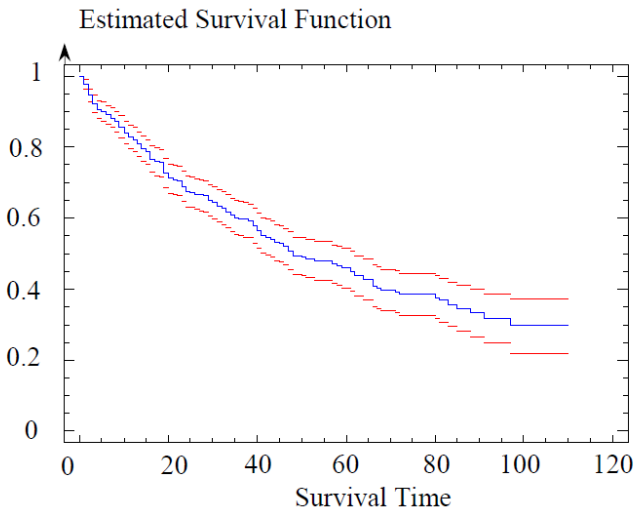

Figure 3. 95% confidence limits for survival function- surgery of colon, all patients.

Table 3. Kaplan-Meier Estimates: colon data

Operation technique	MST	SE
Laparoscopic	64.365	3.184
Open	50.465	3.009

In *Figure 4*, different curves are assigned to different operation techniques.

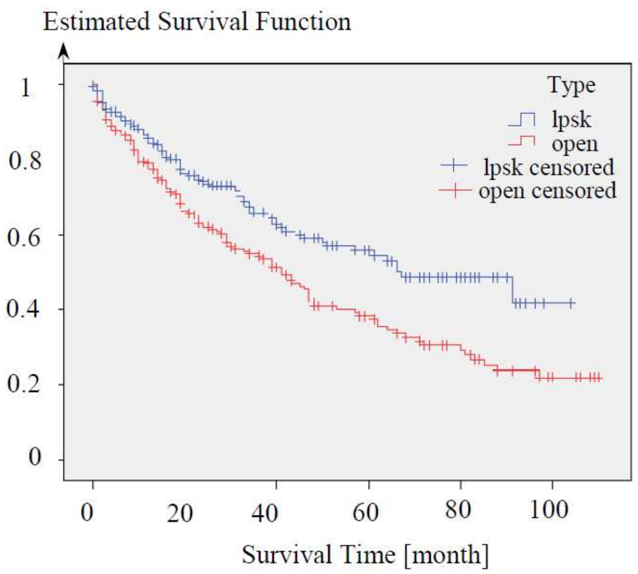

Figure 4. Survival function for surgery of colon.

Table 4. Comparison of groups

Group	Total	Dead	Withdrawn	Withdrawn [%]
Lapar	267	89	178	66.67
Open	250	132	118	47.20
Total	517	221	296	57.25

Seeing the log-rank test result (χ^2 = 12.332, *p*-value = 0.000) we are allowed to formulate the following conclusion: since the *p*-value is less than 0.01, there is a statistically significant difference between the groups at the 99% confidence level.

2.4.3. Data from both rectum and colon operations

Data from both Rectum and Colon Operations have been used to construct Kaplan-Meier estimator of survival functions $R(t)$ according to formula (5). Different curves are assigned to different operation techniques, see *Figure 5*. Seven patients underwent both rectum and colon operations so they were included in both groups. That is the reason why there are seven less patient in data from both rectum and colon operations than in data from rectum and from colon operations together.

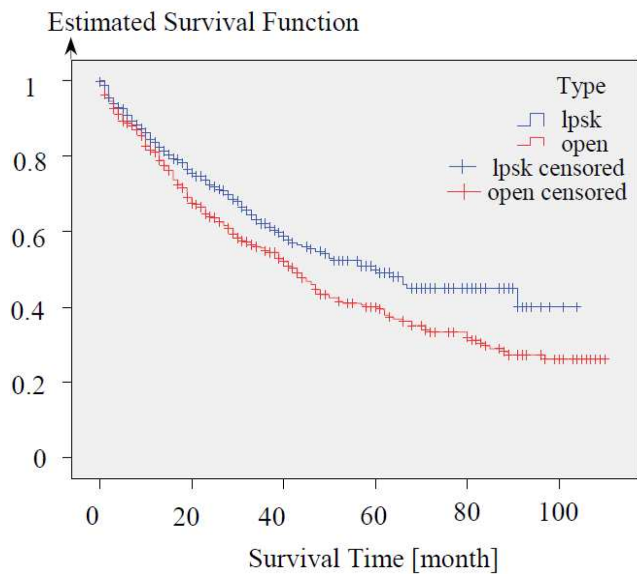

Figure 5. Survival function for surgery of both colon and rectum.

Table 5. Kaplan-Meier Estimates: colon & rectum

Operation technique	MST	SE
Laparoscopic	61.185	2.516
Open	52.938	2.405

Table 6. Comparison of groups

Group	Total	Dead	Withdrawn	Withdrawn [%]
Lapar	455	160	295	64.84
Open	387	205	182	47.03
Total	842	365	477	56.65

Seeing the log-rank test result (χ^2 = 8.070, p-value = 0.005) we are allowed to formulate the following conclusion: since the p-value is less than 0.01, there is a statistically significant difference between the groups at the 99% confidence level.

3. Parametric approach

3.1. Parametric method

Two ageing models are used for the reason of comparison of the two operation techniques. The traditional two-parameter Weibull model [10] and an alternative bi-mode model with three parameters [11] have been used to compare mean survival time of all patients undergoing surgery assigned to individual groups according to operation techniques. The Maximum Likelihood Estimation method applied to randomly censored sample data is used for the parameter estimation (ML Estimators) in both ageing models.

3.1.1. One-mode model (2P-Weibull)

The 2-parameter Weibull model is one of the most widely used lifetime distributions in reliability applications. It is a flexible distribution that can take on the characteristics of other types of distributions, based on the value of the shape parameter β_1. Depending on the values of the shape parameter, we can describe all three life stages of the bathtub curve of the model. For instance, a decreasing failure rate, which represents early dead events, is modeled by $\beta_1 < 1$.
The scale parameter, η_1 (eta), represents the characteristic life of the patient. Other words, it is the time, when approximately 63 % patients end their life.
The failure rate of the 2-parameter Weibull model can be written as follows:

$$\lambda_1(t) = \frac{\beta_1}{\eta_1} \cdot \left(\frac{t}{\eta_1}\right)^{\beta_1 - 1} \tag{10}$$

3.1.2. Two-mode model (3P-BiWeibull)

We will also use an alternative more general bi-mode model with three parameters. The failure rate is modeled by

$$\lambda_2(t) = \lambda_o + \frac{\beta_2}{\eta_2} \cdot \left(\frac{t}{\eta_2}\right)^{\beta_2 - 1} \tag{11}$$

The bi-mode model relies on an exponential distribution (constant failure rate) to describe the random death of patients, and on a two-parameter Weibull distribution to describe their ageing. When λ_0 = 0, the ageing model (11) reduces to the 2-parameter Weibull law (10).

3.2. Results with survival data

In case of open surgery technique obtained results assigned to both Weibull models are very similar and consequently the simpler One-mode model is more useful.

Table 7. Results of open operation technique

	2P-Weibull	3P-BiWeibull
MLE of Scale	65.997	65.998
MLE of Shape	0.9	0.9
1/lambda	-	4.506e7
Mean Survival Time	69.29	69.291

In case of laparoscopic surgery technique obtained results assigned to both models are similar as in previous result. Once again, we are allowed to use the One-mode model which is simpler.
The results demonstrated in *Tables 7-8* show that in both operation techniques the shape parameter is less than 1 what means that these patients are recovering after their operation as if they were in "infant mortality" period of their life. Other words, if the patient overcomes a postoperative complication his/her life should be stabilized.

Table 8. Results of laparoscopic operation technique

	2P-Weibull	3P-BiWeibull
MLE of Scale	88.427	88.428
MLE of Shape	0.91	0.91
1/lambda	-	4.2784e8
Mean Survival Time	92.229	95.711

4. Conclusions

Using both parametric and non-parametric approach we confirmed that laparoscopic surgery for cancer of both rectum and colon is minimally equivalent alternative to open surgery.
On the basis of the data from colon operations as well as joined data from both colon and rectum operations we can conclude that there is a statistically significant difference between the

survival functions associated to both operation types at the 99% confidence level (survival function associated to laparoscopic data is significantly greater).

Comparing mean survival times of open and laparoscopic operation techniques we obtained the result (in months) that 69.3 < 92.2 (95.7). This means that patients who underwent laparoscopic surgery have their mean postoperative life about 33-38% longer than the ones who underwent open surgery. Of course, this result gives priority to the laparoscopic technique. On the other side the shape parameter of the Weibull distribution derived from both techniques is a little less than 1 what signifies an existence of postoperative complications. This situation can be compared with “infant mortality period” of human life which is characterized by decreasing hazard function. Indeed some deaths are observable at that period but the process has decreasing trend, as patients are recovering after their surgery that could be compared to “reborn”. In addition the shape parameter is close to 1 what means that the hazard function decreases very slowly so that patients are close to steady period.

Censored life data were tested on two models including bi-modal Weibull model. Obtained results do not evidence presence of a second factor that would explain the data. Parameters estimated for both one-mode and two-mode models are comparable, so that we can conclude that the simpler two parameter Weibull model is sufficient enough for such kind of analyses.

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