Case Mix Difference Can Affect Evaluation of Outcome of Treatment for Colorectal Cancer

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Abstract. *Aim: To explore the potential effects of patient selection, for example by organization, on survival as outcome parameter in colorectal cancer treatment. Patients and Methods: The main cohort was identified in a Hospital-based registry and outcome data of all 2,717 patients operated on for colorectal cancer between 2000-2011 were evaluated. A simulation of different center settings was performed using several potential selection criteria, including emergency cases, referral surgery and palliative resection, and used for comparison of outcome data. Results: Overall survival and cancer-specific survival can be significantly affected in both short-term (30-/90-day) mortality and long-term survival by factors of organizational level. Conclusion: Survival data as an outcome parameter can be affected by the composition of the patient cohort and thus reflect possible selection bias for example due to organization, referral patterns and practice customs. This potential bias should be acknowledged when making inter-hospital comparisons of outcome.*

All forms of medical treatment have an outcome. It could be the cure of a simple but bothersome urinary tract infection, or the healing of a sutured skin laceration. Colorectal cancer treatment, where surgery provides the main chance of cure, is often more complex and has several outcomes. These constitute a broad spectrum ranging from postoperative infections, through patient-related outcome measures assessing quality of life to the chances of long-term survival (1-3). Their definitions and thus the reporting of many of the named factors is not always fully-consistent and therefore difficult to assess and use for comparisons, as described by Whistance *et al*. (4).

Despite potential difficulties, a surgical facility should have some means of assessing conditions managed and the attained results. The aim then should be to improve on all levels; technical surgical skill, intervention timing and optimization of patients and perioperative conditions to name but a few. Anesthesiology and postoperative care are also of importance where enhanced recovery programs have been shown to facilitate the patient's return to normal functioning (5, 6). Whilst functionality scores could be at the more subjective end of the spectrum, survival data are commonly seen as hard outcome measures. However, there exist several different survival parameters such as overall (OS), disease-free, and cancer specific (CSS) survival, each with its own limitations and advantages. The fact that mortality over time will reach one hundred percent has to be handled, thus raising the question if all outcome parameters are suitable in all situations.

There could be other factors behind the survival figures apart from the skills of the individual surgeons. Survival parameters might be affected for example by the demographic composition of the Hospital's catchment area (7). The risk of cancer stage migration is well-known in the work of pathologists, and affects the survival in patients with stage II and III colorectal cancer (8). Another important factor is the proportion of emergency cases which have been shown, at group level, to have a worse outcome (9). The hypothesis of this study was that patient selection, also by organizational factors, can affect outcomes on the Hospital level. The aim of the study was to explore the potential effects of such selection mechanisms on parameters of survival outcome in patients with colorectal cancer.

Patients and Method

The study was set at Sahlgrenska University Hospital/Östra, Sweden. The unit provides all colorectal cancer surgery for the city of Gothenburg, which translates to a catchment area of approximately 540,000 individuals, as well a regional responsibility for advanced cancer, where the catchment area approximately 1.75 million. There has been a continuous and prospective registration of all procedures for colorectal cancer since 1999. The registry includes demographic and pathological data, as well as treatment information. Follow-up data and survival are also included. Recurrences and deaths are noted. Cause of death is for registry

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purposes noted as cancer-related if there is doubt. The registry, and studies related to it, has been approved by the regional Ethical Review Board.

For the present study, the main cohort (group A) included all patients treated with surgical resection for colorectal cancer during 2000-2011. Demography and outcome were studied in relation to survival, 30- and 90-day mortality, and risk of recurrence. A stepwise simulation was then performed with gradual selection creating alternative cohorts enabling statistical assessment of survival, both OS and CSS, and the aforementioned parameters in the original cohort and possible scenarios. The first alternative, group B, simulates the scenario of an elective center by excluding the emergency cases. The second alternative, group C, simulates a scenario where the unit in A does not have referrals for advanced cancer by also excluding patients with locally advanced T4 tumors. The last, group D, explores the possible impact of the degree to which palliative surgery is performed at the unit by also excluding patients with stage IV disease.

Statistics. JMP 8.0/SAS software (SAS Institute, Inc, Cary, NC, USA) was used for statistical analysis. Survival was assessed by Kaplan–Meier and log-rank test for differences. Other parameter differences were assessed by parametric statistics as appropriate. The significance level was set at 0.05.

Results

The median age was 69 years, with a wide range and even gender distribution. None of the factors were significantly different between the groups but high age was related to non-cancer-related deaths (mean 73 *vs*. 79 years, $p<0.01$). Almost 15% of colon cancer cases had an emergency presentation and therefore affected the proportions of colonic and rectal cancer between group A and B-D. The emergency cases were associated both with higher postoperative mortality and the risk of not attaining radical surgery (Table I). The median observational time of the cohort was nine years for the aspect of survival assessment. The chances of OS differed significantly between the groups, with the best outcome results being obtained for group D. Major improvements were noted (Table I) regarding both local radicality of surgery and survival if not performing surgical resections for stage IV disease (group D *versus* group C). The survival differences remained when comparing OS and CSS (Figure 1).

Table I. *Demographic and outcome data by simulated hospital type (group).*

	Group				
	A	B	C	D	*p*-Value
Characteristic	All	Elective	No referral	No palliative	
No. of patients	2717	2309	1853	1664	NA
Age (range), years	69 (16-96)				
Male/female (%)	50.1/49.9	50.6/49.4	51.6/48.4	50.8/49.2	NA
Site: colon/rectum (%)	64.3/35.7	59.9/40.1	57.5/42.5	58.2/41.8	NA
Radical surgery (%)	84	87	89	99	<0.001
30-Day mortality (%)	2.1	1.4	1.4	1.3	0.07
90-Day mortality (%)	5.0	3.6	3.6	2.0	<0.001
Risk recurrence (%)	25.3	22.7	20.4	20.0	<0.001
Alive at time of study (%)	51	54	58	64	<0.001

NA: Not applicable

Discussion

In the quese for good results it is crucial to focus on improving health care of the individual patient, not improvement of health care unit figures. The relatively poor short- and long-term outcome associated with emergency presentation of colorectal cancer is well-known and has been described, but rarely at an organizational level (9, 10). If our Unit no longer performed emergency resections, for example by deciding that all emergency cases should be referred to another unit, our results could probably improve (Figure 1, going from group A to B). The next issue that could affect our unit's overall results is being a referral center for advanced cancer. T4 tumors often require more extensive surgery and thus carry a higher risk of complications and also have a higher risk of node metastasis, which can have impact on recurrence and survival. As shown in scenario C, a focus on T1-T3 cancer foremost affects long-term results but still at a significant level. Parallel to patients with locally advanced cancer are those with tumors with already established metastases. Herein, as shown by scenario D, palliative resection and combination surgery including resection of metastases could significantly tweak the survival outcome. Still, resection surgery can at times ameliorate the patient's condition and often has a place in clinical practice more than simply improving survival (11).

Also influencing survival data in multiple ways are the great advances of modern medicine. These provide the opportunity to treat more patients and more difficult conditions. Related to this, improvements in anesthesiology have facilitated surgery for older patients with higher degrees of co-morbidity compared to 20 years ago. As noted for the age aspects, the definition of old varies and is changing (7). High age, also being associated with different degrees of comorbidity, was duly noted to be associated with a higher chance of a non-cancer-related death in concordance with previous studies (10, 12). Thus, there is a notable difference in survival between OS

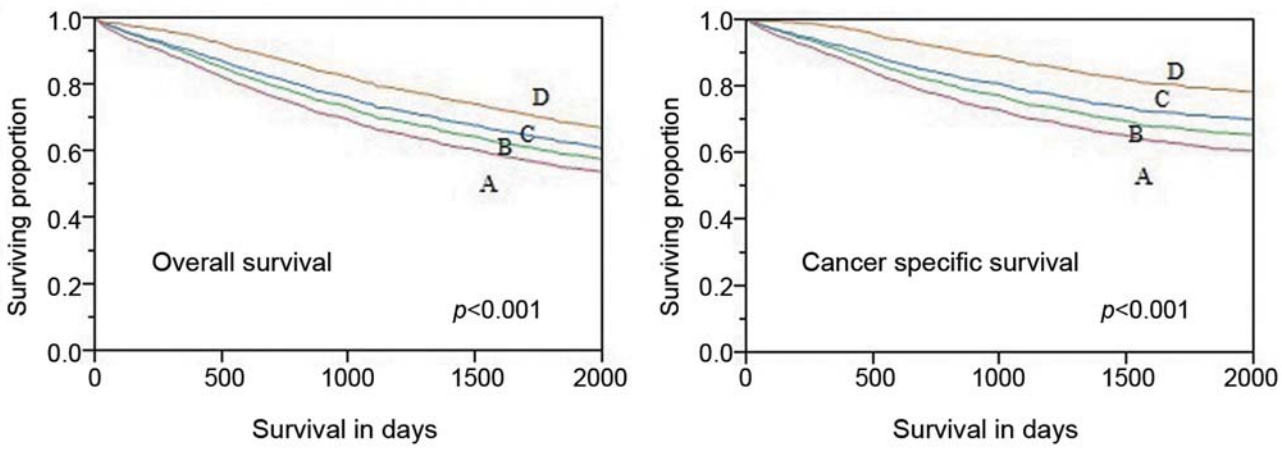

Figure 1. *Overall and cancer-specific survival data by simulated hospital type. A: Current case mix; B: No emergency resections; C: No T4 resections; D: No palliative resections*

and CSS (Figure 1). Here it is important to bear in mind that the demographic data affect the use of OS data and can also have regional or international variations. An interesting example taking this into consideration is the use of age-relative and stage-specific survival in the data from the National Swedish Colorectal Cancer Registry (13). Thus, there might be more suitable outcome parameters for cancer surgery for our oldest clientele than 5-years OS.

Data acquisition can be readily made, but the real challenge is data interpretation and utilization. Hence, comparing data between hospitals, regions and countries must be done with caution (1). Differences in patient demographics, health policies, economics and registration can affect perceived outcomes. There are studies noting the difficulties interpreting outcome when comparing hospitals, such as that by Abdelsattar *et al*. (1). There are other studies where the challenges are acknowledged and efforts were made to statistically adjust for this (14). On a regional level, other resources, such as pathology services, have been shown to affect stage-specific prognosis. Even if to some degree this is due to stage migration effects, it could also partly be due to true impact on survival. At the more local level, as shown in this study, organizational issues cannot be considered to be negligible. The possibility of the same selection mechanisms enhancing results might exist and should not be forgotten.

There are several limitations to this study. One is the use of hypothetical and segmental scenarios rather than proven units. Another, by international comparison, is the relatively low number of patients. The aim of the study was, however, to explore differences in outcome and the risk of selection bias. Hence, the importance lies in the group differences rather than the exact figures. Another issue is the probable deterioration of the results of other units needing to handle the emergency or non-referred patients, meaning that a region creating more centers of type D could increase the proportion of patients with poorer prognosis at type A units, whose results would in turn worsen. Another possibility is of course that these patients would not get be operated on at all. Thus, confronted with the obvious question of which hospital type (A-D) you would prefer to be treated at, an important assessment should be if they treat the same patient categories, raising the issue of to what degree the data are comparable. In accordance with this, a straight transfiguration of the data into terminology of quality should only be performed with care and modesty, given difficulties shown in data interpretation. Even more care should be taken before allowing such outcome data to affect the health economics at an organizational level. Reimbursement systems may provide incentives for patient selection favoring good outcome. This could potentially lead to a quest for good results that do not benefit patients with advanced tumor or emergency presentations. The example in the study was surgical resections for colorectal cancer. However, these results could plausibly be translated not only to other malignant diagnoses but also to common procedures such as hernia surgery and cholecystectomies, when studied at the group level. In short, selecting patients with better prognosis is likely to produce better results. Thus, the structure or organization within a healthcare system may provide a type of selection bias.

Conclusion

Outcomes of colorectal cancer resections in terms of OS and CSS can be affected by the composition of the patient cohort and thus introduce possible selection bias. This potential bias should be acknowledged when making inter-hospital comparisons of outcome.

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