Curative resection for colorectal cancer in the elderly. Prognostic factors and five-year follow-up

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Abstract

The purpose of this perspective study was to evaluate which prognostic factors predict long-term survival and disease-free survival (DFS) of elderly patients (65 years) who underwent surgery for colorectal carcinoma. Between January 1992 and December 1998, 196 colorectal cancer patients 65 years (114M; 82F; mean age: 75 years; range: 65-92) underwent surgery. One hundred forty-five (74%) of them underwent curative surgery and emergency surgery was more common in patients 75 years of age than among those younger than 75 years (39% vs 23%; p = 0.01). The overall peroperative mortality rate was 3% (n = 6). The median length of hospital stay was 18 days (range: 3-86 days). By univariate analysis, intraoperative bleeding (500 cc; p = 0.002), length of surger y (240 min.; p = 0.004), and rectal cancer (p = 0.0001) were associated with complications. By multivariate analysis, only rectal cancer (p = 0.002) was associated with complications. The overall 1, 3-, and 5-year survival rate and DFS rate were 97%, 82%, 74%, and 86%, 64% and 60% respectively. Using multivariate analysis only tumour stage (p < 0.0001) and peroperative blood transfusions (500 cc; p = 0.006) w ere associated with outcome. Treatment decisions in elderly patients with colorectal carcinoma should not be influenced by the chronologic age of the patient.

Key words: Colorectal carcinoma, colorectal surgery, risk factors, survival, elderly patient.

Riassunto

TRATTAMENTO CHIRURGICO RADICALE PER CARCINOMA DEL COLON-RETTO NEL PAZIENTE ANZIANO. FATTORI PROGNOSTICI E SOPRAVVIVENZA A CINQUE ANNI

Scopo di questo studio è stato quello di identificare ed analizzare i fattori prognostici in grado di influenzare la sopravvivenza in una serie consecutiva di pazienti con età 65 anni affetti da carcinoma del colon-retto e sottoposti ad intervento chirurgico. Tra il Gennaio 1992 ed il Dicembre 1998, 196 pazienti con età 65 anni (114 M; 82F; età media: 75 anni; range: 65-92) affetti da carcinoma del colon-retto sono stati sottoposti ad intervento chirurgico. In 145 casi (74%) è stato effettuato un intervento oncologicamente radicale, mentre l'intervento chirurgico d'urgenza è stato più frequente per i pazienti con età 75 anni. La mortalità peroperatoria è stata del 3%. La degenza media è risultata di 18 giorni (range: 3-86). Dall'analisi univariata il sanguinamento intraoperatorio (

Introduction

The increasing incidence of colorectal carcinoma in Western countries, its high pre valence in the elderly, and the aging of the population have given rise to considerable interest in the assessment of curative treatment outcomes for this disease in the aged. This evaluation is most important in the very elderly patient, in whom the increased operative risk, the need for a longer hospital stay, and expensive post-operative care must be weighed against the limited prospects of surv i val, leading to doubt as to which is the best therapeutic policy.
In the last decade, several Authors have addressed this topic (1-8), although only a proportion of them have reported the long-term survival rates in the very elderly. Although these rates are usually compared with the rates of younger patients, an emphasis on the concept that survival in the elderly patients should also be related to the demographic life expectancy is lacking in the literature. This would provide a basis for any further evaluation about the actual oncologic results and the risk to benefit or cost to benefit ratios.
The purpose of this study was to analyze which prognostic factors predict survival and disease-free survival on 65 years old patients with colorectal cancer who underwent curative surgery.

Patients and methods:

A consecutive series of patients aged 65 years or older who were diagnosed with and treated for primary colorectal cancer at the Department of Emergency Surgery at University of Milan – S. Raffaele Scientific Institute

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500 cc; p = 0.002), la durata dell'intervento (240 min.; p = 0.004) ed il carcinoma del retto (p = 0.0001) sono risultati associati ad una maggiore incidenza di complicanze post-operatorie. Dall'analisi multivariata solo il carcinoma del retto (p = 0.002) è risultato associato ad una maggiore incidenza di complicanze post-operatorie. La sopravvivenza e l'intervallo libero da malattia neoplastica registrate ad 1, 3, e 5 anni sono risultate del 97%, 82%, 74% e dell'86%, 64% e 60% rispettivamente. Dall'analisi multivariata lo stadio della neoplasia (p < 0.0001) e le emotrasfusioni (500 cc) (p = 0.006) sono risultate correlate con la sopravvivenza.

Il trattamento chirurgico resettivo quando possibile, rappresenta ancor oggi la terapia di scelta per il paziente affetto da carcinoma del colon-retto, e l'età non deve di per sé costituire una controindicazione alla terapia chirurgica.

Parole chiave: Carcinoma del colon-retto, chirurgia del colon-retto, fattori di rischio, sopravvivenza; Paziente anziano.

between January 1992 and December 1998, was evaluated. Data from 196 patients were extracted from the data base, hospital and office charts. One hundred and forty-five (74%) of them underwent curative surgery.

Curative resections were defined as those that were performed without histologic or substantial clinical evidence of residual tumour.

At the end of the observation period, 62 patients (32%) has died, and 134 (68%) were alive. Clinical information on the patients was related to outcome. Modified Dukes classification was used (9).

Routine follow-up was every 4 months for 2 years and every 6 months thereafter.

Operative data, antibiotic prophylaxis, transfusions, tumour stage, time of operation, morbidity and perioperative mortality (within 30-day following surgery), recurrence and death, were analyzed. The length of hospital stay was evaluated for the period related to primary treatment. Overall survival and disease-free survival (DFS) were calculated from the date of surgery.

A resection was considered as an emergency when it was performed as the first surgical step, rather than after colostomy for complicated tumour.

The American Society of Anesthesiologists (ASA) Physical Status Scores have been defined previously (10).

Analysis of the data:

Statistical analysis was carried out with the Pearson Chi-squared test or Fisher's exact test for univariate analysis. Since the distributions of length of hospital stay and post-

Tab. I – LENGTH OF HOSPITAL BY SOME DEFINED VARIABLES

Variables	*Pts n.*	*Median stay (days)*	*Mean rank*	*p*
ASA score				
II or III	166	21	101.13	
IV	30	17	80.09	0.07
Symptoms				
Anaemia or blood mixed with stools	46	23	113.54	
Age in years				
65-74	117	18	97.87	
75	79	20	99.44	0.85
Sex				
Male	114	20	94.77	
Female	82	21	103.68	0.28
Site of tumour				
Colon	141	19	89.17	
Rectum	55	24	122.42	0.0002
Curative surgery				
Yes	145	21	100.85	
No	51	19	71.82	0.33
Turnbull's stage				
A or B	87	22	104.45	
C or D	109	19	93.75	0.19
Operation				
Tumour resection	186	20	97.67	
Palliative treatment	10	21	113.85	0.38
Peroperative blood transfusions				
500 cc	166	20	95.38	
> 500 cc	30	24	115.75	0.07
Bleeding				
500 cc	161	20	95.06	
> 500 cc	35	23	114.46	0.07

Tab. II – POST-OPERATIVE COMPLICATIONS BY DIFFERENT VARIABLES. UNIVARIATE ANALYSIS

Variables	*Pts n.*	*Postoperative complications %*	*p*
All patients	196		
ASA score			
II	84		
III	82	31 (2 + 3)	
IV	30	36 (4)	0.56
Age in years			
65-74	117	26	
75	79	42	0.02
Timing of surgery			
Elective surgery	138	33	
Emergency surgery	58	29	0.58
Sex			
Male	114	32	
Female	82	33	0.91
Site of tumour			
Colon	141	23	
Rectum	55	55	0.0001
Curative surgery			
Yes	145	34	
No	51	25	0.24
Turnbull's stage			
A or B	87	36	
C or D	109	28	0.21
Blood transfusions			
500 cc	166	29	
> 500 cc	30	46	0.06
Bleeding			
500 cc	161	27	
> 500 cc	35	54	0.002
Length of surgery			
240 minutes	157	43	
> 240 minutes	39	20	0.004

operative care were highly asimmetrical the median values are presented and the Mann-Whitney U-Wilcoxon Rank Sum W test was used for tests of equalities.
Survival was calculated with Kaplan-Meier method using the Log-rank test for comparing the survival distributions in different strata with a maximal follow-up time. The Cox regression model with forward stepwise selection based on likelihood ratios was used for multivariate regression analysis of the survival distributions.
All p values less than 0.05 was considered to be statistically significant.

Results

A total of 196 patients older than 65 years had been operated on for colorectal carcinoma (114 men, 82 women; mean age: 75 years; range: 65-92 years). Eighty four patients (43%) had an ASA grade II; 82 patients (42%) had an ASA grade III, and 30 cases (15%) had an ASA grade IV. One hundred thirty eight patients (70%) of the 196 cases underwent elective surgery, while 58 cases (30%) underwent emergency operation. Of the elective surgery, 73% were curative. Emergency operations were more common among patients over 75 years of age than among those younger than 75 years (39% vs 23%) (p = 0.01). Among the male patients the proportion of rectal carcinoma was slightly larger than among the female (32% vs 22%) (p = NS).
The median length of hospital stay was 18 days (range: 8-36 days). Only 9 patients (5%) required admission to the intensive care unit (ICU) and the median length of ICU was 14 days (range: 1-39). Pre-operative anaemia and/or blood mixed with stools (p = 0.03), and rectal carcinoma (p = 0.0002) were significantly associated with an increased length of hospital stay (Tab. I). By univariate analysis, 75 years or older (p = 0.02), peroperative bleeding (500 cc) (p = 0.002), length of surgery (240 minutes) (p = 0.004), and rectal carcinoma (p < 0.0001), were strongly associated with higher incidence of post-operative complications. There were no significant difference of complications after emergency operations than after elective surgery (Tab. II).

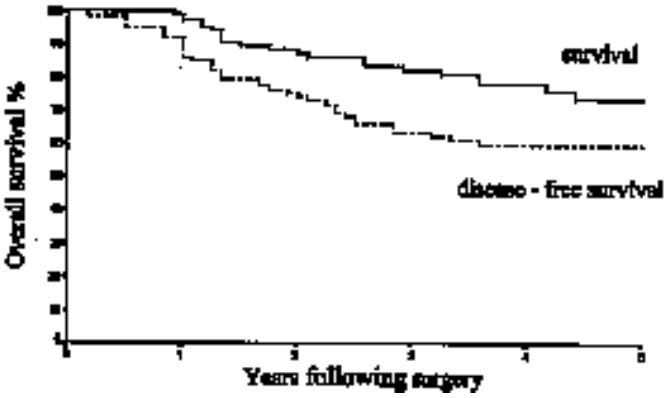

Fig. 1: Survival and disease-free survival for patients 65 years of age who underwent curative surgery for colorectal carcinoma at S. Raffaele Hospital between January 1992 and December 1998.

The overall perioperative mortality rate was 3% (n = 6). Three patients died from septic shock and multiple organ failure syndrome. One case of them died following diffuse peritonitis, and 2 patients following leakage from a left colonic anastomosis. Two patients died from liver failure and 1 case died from myocardial infarction.
With so few deaths, analysis for predictors of death was not appropriate.

Survival and long-term outcome:

The overall 1-, 3-, and 5-year specific survival rate and disease-free survival rate were 97%, 82%, 74%, and 86%, 64%, and 60% respectively (Fig. 1).
The overall 1-, 3-, and 5-year specific survival rate was 97%, 79%, and 69% for patients who underwent an elective surgery, and for patients who underwent emergency operations were 97%, 90%, and 84% respectively (p = 0.2) (Tab. III).
By multiple logistic regression analysis, only tumour stage (p < 0.0001) and perioperative blood transfusions (p = 0.006) were associated with outcome (Tab. IV).
ASA grading and chronological age were not associated with outcome.

Tab. III – FIVE-YEAR SPECIFIC SURVIVAL BY DIFFERENT PRE-OPERATIVE PATIENT VARIABLES

Variables	*Pts n.*	*% after 5 years*	*p*
Curative surgery	139	74	
ASA score			
II	61	76	
III	60	72	0.9
IV	18	72	
Symptoms			
Anaemia or blood mixed with stools	32	76	NS
Timing of surgery			
Elective surgery	108	69	
Emergency surgey	41	84	0.2
Sex			
Female	83	74	
Male	56	74	0.6
Age in years			
65-74	81	74	
75	58	75	0.7
Site of tumour			
Colon	95	77	
Rectum	44	68	0.4
Turnbull's stage			
A	12	100	
B	72	90	
C	46	50	
D	9	0	0.0001
Peroperative blood transfusions			
500 cc	120	77	
> 500 cc	19	48	0.01
Postoperative complications			
No	95	73	
Yes	44	76	0.9

Tab. IV – COX REGRESSION ANALYSIS OF VARIABLES INFLUENCING SPECIFIC SURVIVAL IN COLORECTAL-CANCER PATIENTS OF 65 YEARS OF AGE

Variables	*p*	*Hazard ratio*	*95% CI*
Turnbull's stage	0.0001	5.5	2.9-10.6
Peroperative blood tranfusion >500 cc	0.0065	3.9	1.5-10.3

Discussion

The prognosis of colorectal carcinoma is clearly related to the stage of the tumour at the time to discovery. Reports throughout the world confirm that up to 40% of all colorectal carinoma patients are beyond a definitive cure because the cancer has already spread either locally or distally at the time of diagnosis (11-13).

In this study of old and very old patients with colorectal carcinoma, an overall perioperative mortality rate of 3% is relatively low, but in accordance with other similar results from the same period of time (7). The overall specific survival among all patients was 74%. This is figure that is well in line with the survival in other studies (14-16).

Old and very old patient has been previously described as a factor that provokes controversy in the ASA scoring among anaesthesiologists. Even though some bias in our ASA scoring cannot be completely ruled out, the ASA grade was not significatively associated with survival. In our series of patients, by univariate analysis, all patients with 75 years of age or older, intraoperative bleeding, the length of surgery and rectal carcinoma, were all associated with higher incidence of post-operative complications. However, in our study, in disagreement with others (1, 17), the emergency operations was not associated with morbidity and mortality. The results of previous reports regarding age have been variable. Some Authors have reported similar results (18-20), while other have shown age to be a determinat of one or more of the above outcomes (15, 21-24).

By multivariate analysis, only perioperative blood transfusions (500 cc) and tumour stage according to a modified Duke's classification were confirmed as prognostic factors for long-term survival. The spread of the tumour was the most important prognostic factor. The metastatized cancer predict a poor survival. It is notable that as many as 25% of patients with Dukes B carcinoma died within 5 years. This shows that non-visible metastases exist in many cases, although the carcinoma seems to be radically curable at surgery, and the small size of the tumour seems to be a good prognostic sign. In fact, it has been shown previously that small carcinomas usually represent nonmetastatized Dukes stages and that the main symptom with these small tumours is blood mixed with stools, either obvious or occult (13).

In conclusion, in our study peroperative mortality rate is very low and is comparable with other reports (12, 25, 26). Old age *per se* should not deter us from offering patients the best surgical treatment, without any consideration of their chronologic age.

The spread of the cancer at the time of diagosis is the most important prognostic factor for outcome. By thorough pre-operative assessment, and by skilled and careful surgery to minimize complications and bleeding, the perioperative morbidity and mortality rate may be kept at a low level even in this series of old and very old patients.

Surgical resection is still only the best chance of potentially curative therapy for colorectal carcinoma, and the best way to palliate patients with incurable colorectal cancer. Treatment decisions in elderly patients with colorectal carcinoma should not be influenced by the chronologic age of the patient.

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Commento Commentary

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Questo è un lavoro retrospettivo nel quale gli Autori hanno rivisto la propria casistica per cercare di identificare ed ana - lizzare i fattori prognostici che possano influenzare l'andamento clinico e la sopravvivenza negli anziani operati per tumo - re colorettale.
La conclusione è che l'età non deve di per sé costituire una controindicazione alla terapia chirurgica.
Il lavoro è metologicamente corretto e rafforza un concetto che riteniamo dovrebbe essere ormai accettato ed applicato nella pratica clinica. Non viene fatta menzione di eventuali trattamenti adiuvanti di tipo radio o chemioterapico e, per essere il campione costituito da oltre il 50% di pazienti (esattamente 109) con malattia in stadio C e D è rilevante la sopravvivenza a cinque anni (74%). Bisogna tuttavia notare l'appiattimento della curva dopo i tre anni che è forse dovuta al follow-up troppo breve per i pazienti arruolati negli ultimi due anni (casistica fino al Dicembre 1998). Un calcolo della "cruda sopravvivenza" sarebbe forse stato più rispondente alla realtà.
È apprezzabile lo sforzo degli Autori per far giungere, soprattutto ai chirurghi più giovani il messaggio di non lasciarsi influenzare, nella decisione chirurgica dalla età avanzata che, come hanno dimostrato, non influenza i risultai clinici. Il lavoro dimostra inoltre come le complicanze ed il sanguinamento intraoperatorio assumano, soprattutto in questi pazien - ti un ruolo di grande importanza.

This is retrospective study in which authors rewieved patients records to evaluate which prognostic factors predict the clinical outcome and long term survival in elderly patients undervent surgery for colorectal cancer.
The conclusion is that the treatment decisions making should not be influenced by the chronologic age of the patients.
The paper is well done and remarks somethingh which should be accepted and applicated in the routinary clinic.

Radio-chemotherapy as adjuvant treatment is not reported even if more than 50% of patients (109) were affected by stage C and D cancer but the overall specific survival among all patients was anyway high (74%).
Looking the survival curve, which is liner after the third year for the short follow-up, it may be the crude survival should be more rappresentative of the reality.
It is remarkable the efforts of the authors to underline that old age per se should not deter from offering patients the best surgical treatment because the clinical outcome is not influenced by chronologic age of the patients.

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