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A Study of Aspects on Gender and Prognosis in Synchronous Colorectal Cancer

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Abstract:
Aim: To assess differences in demography, pathology and prognosis with tumor multiplicity in colorectal cancer.
Method: A retrospective single centre study of all patients surgically treated for a colorectal cancer during 1999–2008 (n = 2524). Patient characteristics, pathology and follow-up data were retrieved. Survival was assessed by overall and cancer specific survival.
Results: 60 (2.4%) patients had a synchronous cancer (SC), associated with right colon, higher age, more assessed lymph nodes but a lower frequency of stage III/IV disease (42% vs. 52%). There was no overall prognostic difference between single or multiple cancer patients but females with SC had better survival than corresponding males ($P < 0.046$).
Conclusion: The incidence of synchronous cancers was 2.4% with the second cancer often located in right colon. The SC patients were older than single tumor patients, had a lower frequency of stage III/IV disease and the females with SC had a better survival prognosis than corresponding males.

Keywords: gender, colorectal cancer, multiple tumors, mortality, survival

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Introduction

Colorectal cancer is a common cancer form in Sweden and the incidence is slowly increasing.[1] There is a known risk that a patient can have a second coexisting colorectal cancer.[2] Thus, most treatment guidelines include some type of colon examination in the preoperative work-up to provide the information and enable an optimizing the surgical procedure.[3] This is performed parallel to the staging procedure which is aimed at identifying metastatic presence and thus for the strategic therapeutic decisions.[4] A failure in attaining a full bowel exam could mean a risk of not attaining radical surgery or even fatally delaying the finding and treatment of the second cancer.

The term synchronous cancer (SC) is used when there was more than one cancer at the same time. Each tumor should also have a separate and definite picture of malignancy and they should also be separated by macroscopically normal bowel wall. The risk of SC in colorectal cancer has been reported at 2%–3%.[2,5] Some known risk factors such as familiar polyposis and ulcerative colitis with dysplasia could increase the risk.[6] Some studies have also found an increased frequency of multiplicity in male patients.[7,8] The term synchronous cancer should be distinguished from both metachronous cancer (MC) which occurs later and anastomotic recurrences by their location. The risk of developing a second and thus metachronous cancer has been reported as increased and a colon surveillance should thus be undertaken postoperatively.[9,10]

The influence by cancer multiplicity on the survival prognosis in colorectal cancer is less studied. Most reports on this subject have not shown any significant survival difference between single and multiple colorectal cancers.[11–13] To our knowledge, no study has assessed any gender-related differences in prognosis with multiple cancers. Still, there are several reported findings regarding the difference in prognosis between male and female patients with single tumor colorectal cancer.[14,15] The aim of the study was to assess the influence of tumor multiplicity on prognosis in colorectal cancer. Secondary aims were to identify associated prognostic factors and possible gender difference in survival after multiple cancers.

Patients and Methods

The study was a retrospective analysis of all patients surgically treated for a colorectal adenocarcinoma during 1999–2008 (n = 2524) at a single centre university hospital. The study was conducted along ethical guidelines and approval by the ethics committee. Patient characteristics like gender and age were retrieved along with pathology data (location of tumor, stage, lymph nodes, grading and possible tumor multiplicity). Both synchronous and metachronous cancers and their incidence were identified during the studied period. The 5th edition of the TNM classification was used for tumor staging purpose during the period.[16] For the patients having multiple tumors, the one with the most advanced tumor stage was recorded and considered as main tumor for the study. For multiple tumors was the differentiation of main lesion used in the study. The patient characteristics were analyzed both by tumor multiplicity and by gender. Survival was assessed for the cohort with tumor multiplicity. The outcome parameters used was overall survival (OS) and cancer specific survival (CSS).

Statistical analysis

Statistical analyses were performed using JMP 8.0 software (SAS inc., Cary, NC, USA). Statistical tests performed included chi-square, independent-samples t-test or ANOVA. All parametric tests showing statistical significance were also controlled with non-parametric methods due to the size of the SC cohort. Survival was assessed by Kaplan Meier and comparisons between groups by log-rank test. A Cox proportional hazard analysis was performed for CSS both overall and in the SC cohort including prognostic factors significant in univariate survival analysis. Findings with two-sided P-values <0.05 were considered statistically significant.

Results

Patient characteristics

Of the 2524 assessed patients, 2464 (97.6%) had a single tumor and 60 (2.4%) had a second, synchronous, tumor. 38 patients (1.5%) developed a metachronous tumor during the follow-up. The patients' characteristics grouped by tumor multiplicity are summarized in Table 1. The patients with SC cancers were significantly older than the single carcinoma patients ($P < 0.026$). The postoperative hospital stay was also longer ($P < 0.0047$) due to more extensive surgical procedures. There was no difference in differentiation grade,

Table 1. Patients characteristics by tumor multiplicity in a patient cohort operated for colorectal adenocarcinoma (n = 2524).

Characteristics	Single carcinoma group (n = 2464)	Double carcinoma group (n = 60)	Statistics
Age (mean ± sd)	69.2 ± 0.3	72.9 ± 1.6	$P < 0.026$*
Gender (M/F)	1220/1244	35/25	$P < 0.17$
Colon/Rectum (n)	1531/933	37/23	$P < 0.91$
Stage I/II/III/IV	275/833/869/409	12/23/17/8	$P < 0.070$
Grade: high/medium/ low/undiff	119/1624/484/153	3/43/10/4	$P < 0.91$
Assessed nodes (mean ± sd)	15.9 ± 0.2	26.8 ± 1.3	$P < 0.001$*
Positive nodes in stage III (mean ± sd)	3.1 ± 0.1	3.2 ± 0.5	$P < 0.98$
Length of stay (mean ± sd)	11.1 ± 0.2	14.5 ± 1.2	$P < 0.0047$*

Note: Statistical significance ($P < 0.05$) is marked with*.

T-stage or N-stage. With SC it was more likely to have a cancer located in the right colon compared to single tumor location frequency ($P < 0.001$). SC was associated to more assessed lymph nodes ($P < 0.001$) as the resections were more extensive. There was no difference in stage distribution ($P < 0.07$) even though advanced disease (stage III and IV) was less frequent in the SC group (42% vs. 52%, relative risk 0.67). The same pattern was seen for differentiation grade but did not reach significance. The stage of the second tumor was significantly associated to the main tumor ($P < 0.001$). All statistical significances were valid also in non-parametric control tests.

Gender and survival

The median follow-up was 64 months. Data on the SC patients' characteristics are presented by gender in Table 2. There were more males than females with SC but not reaching statistical significance. There were no significant gender related differences in characteristics or tumor pathology in the SC group. Neither was there any difference in tumor location or given treatment. There was no difference in survival regarding multiplicity for the entire cohort ($P < 0.2$). Females with SC had better survival than corresponding males in both OS ($P < 0.036$) and CSS ($P < 0.046$), shown in Figure 1. Age, T and N stage were significant for survival in the multivariate analysis. Gender was significant within the SC cohort also in multivariate analysis ($P < 0.035$). A later development of MC did not affect the stage specific survival.

Table 2. Characteristics of patients with synchronous colorectal cancers (n = 60) shown by gender.

Characteristics	Male (n = 35)	Female (n = 25)	Statistics
Age (mean ± sd)	71 ± 2.3	75 ± 2.6	$P < 0.19$
Colon/rectum (n)	20/15	17/8	$P < 0.53$
Stage: I/II/III/IV	2/11/15/7	2/10/11/2	$P < 0.44$
Grade: high/ medium/low/undiff	1/25/7/2	2/18/3/2	$P < 0.69$
Assessed nodes (mean ± sd)	30 ± 3.7	22 ± 4.3	$P < 0.12$
Positive nodes in stage III (mean ± sd)	4.4 ± 1.6	1.7 ± 1.3	$P < 0.13$

Discussion

The term of multiple colorectal carcinomas commonly include both synchronous (SC) and metachronous (MC) tumors. An important difference is the time frame where SC means coexisting cancers and MC a second and thus later developed cancer. The incidence in our material of 2.4% and 1.5% respectively concur with previous findings.[2,5] Despite the low incidence, they can constitute a clinical challenge as they need to be identified to provide an optimal cancer treatment. The consequence is the need of both a preoperative colon exam to find a possible SC and the postoperative surveillance for MC or anastomotic recurrences. The risk of having a second tumor located in the right colon was high in this material ($P < 0.001$). Thus is a full colonic examination, by radiology or endonoscopy, necessary to negate the presence of a second cancer.

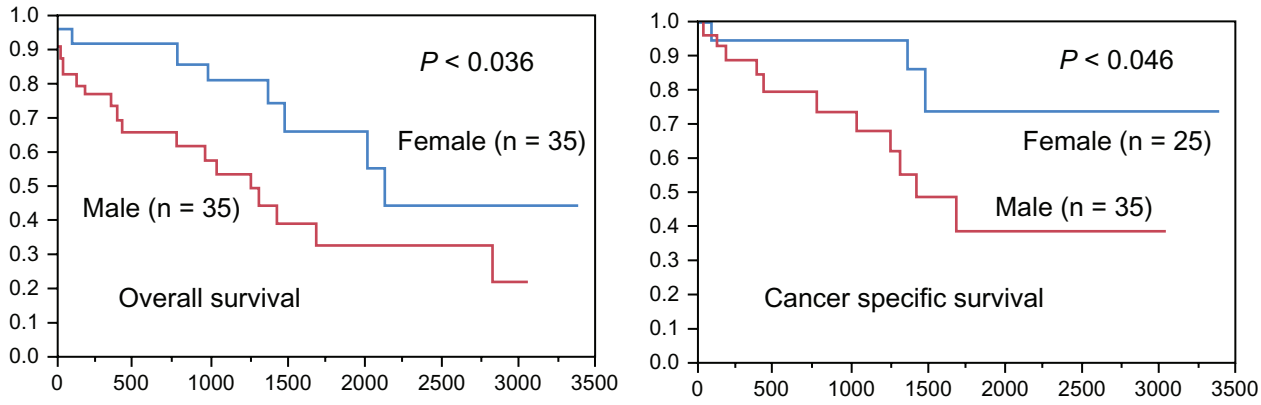

Figure 1. Gender-related difference in overall and cancer specific survival in a cohort (n = 60) of patients with synchronous colorectal cancer.

There were more males in the SC group which is a characteristic that concur with previous findings[7,8] although the difference did not reach statistical significance. The mechanisms underlying gender differences in tumor multiplicity are presently unknown. Hormone effects have been suggested as testosterone can affect the immune function negatively in men and female sex steroids could have a protective immune role in human colon tumors. Estrogen and progesterone receptors in colorectal cancer messenger RNAs coding has also been found.[15] Another characteristic of the SC group is the higher age of the group and foremost of the females. The significantly higher age in this SC material do also concur with other publications.[2,17,18] As females normally have longer life-spans and thus at higher age constitute a higher proportion of the cancer patients it could have been expected to find a higher female representation in the SC cohort. This aspect could strengthen the hypothesis of a higher incidence for males as discussed above.

There was no significant difference in survival between the single carcinomas and the SC cohort. Neither was there any difference any overall cancer stage or stage specific survival. The SC patients were more likely to be operated with more extensive resections and thus yielding higher lymph node assessment counts. Having more than one cancer should hypothetically increase the risk of at least one providing node metastasis and thus higher rates of stage III. However, this was not observed and the frequency of advanced disease (stage III and IV) was even less in the SC group (42% vs. 52%). The absence of statistical difference between single and multiple carcinomas regarding mortality and survival has been previously described.[11,12,19,20] The finding of a better survival, both OS and CSS, for females in the SC cohort is interesting. There was no pathology or staging (Table 2) differences between the genders which could explain the result. One possibility, often difficult to negate, could be a bias due to the longer life expectancy of a female. However, the finding also on CSS could suggest that there could be a survival difference.

Another possible explanation could be in an alternate pathway of carcinogenesis. Jass et al have suggested that colorectal cancer could be a summary of several different entities, each with its' own characteristic.[21,22] The theory involves diverse bio-molecular differences including in Microsatellite instability (MSI) which has been found to be significantly higher in multiple carcinomas.[23–25] Interestingly, one group described by Jass et al develops through serrated polyps rather than adenomas and can be associated to females and high MSI.[22] Other associated findings such as alterations in gene methylation have been reported by Wettergren and Odin, suggesting that there are changes in the bowel mucosa also at longer distances away from the tumor.[26,27] The findings could support a theory of extensive mucosal changes leading to development of multiple carcinomas. Further studies on the bio-molecular properties of the tumors and mucosa could be of great interest. An alternate pathway of cancer development could then hypothetically results in different cancer characteristics and even prognosis. The low incidence of metachronous cancers could suggest that the bio-molecular changes in the mucosa discussed above are reversible.

The study indicates that there could be a gender associated difference in the survival prognosis in synchronous colorectal cancer. As SC also is more common at higher age a possible underlying explanation could be an alternate pathway for tumor development. The patients in the study represent a consecutive, unselected material of which we have valid clinical data. In being a single centre study, they have all been assessed and treated along the same guidelines. Whilst it is, to our knowledge, one of the larger single-centre materials on the subject there is a weakness in the rather small number of SC patients due to a low incidence. We did not further analyze survival and prognosis for the MC patients, which mainly is stage dependent for the second cancer as a MC prerequisite is a good survival from the first. MC and SC are, in our opinion, two separate entities and should thus be handled in analysis and evaluation.

Conclusion

The incidence of synchronous cancers was 2.4% with the second cancer often located in right colon. The SC patients were older than single tumor patients, had a lower frequency of stage III/IV disease and the females with SC had a better survival prognosis than corresponding males.

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Disclosures

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References

1. Socialstyrelsen. *Cancer incidence in Sweden 1999. 2001*. 2001, Swedish National Board of Health, Stockholm.
2. Welch JP. Multiple colorectal tumors. An appraisal of natural history and therapeutic options. *Am J Surg*. 1981;142(2):274–80.
3. Fante R, Roncucci L, Di Gregorio C, et al. Frequency and clinical features of multiple tumors of the large bowel in the general population and in patients with hereditary colorectal carcinoma. *Cancer*. 1996;77(10):2013–21.
4. Kehoe J and Khatri VP. Staging and prognosis of colon cancer. *Surg Oncol Clin N Am*. 2006;15(1):129–46.
5. Cunliffe WJ, Hasleton PS, Tweedle DE, Schofield PF. Incidence of synchronous and metachronous colorectal carcinoma. *Br J Surg*. 1984;71(12): 941–3.
6. Box JC, Rodriguez-Bigas MA, Weber TK, Petrelli NJ. Clinical implications of multiple colorectal carcinomas in hereditary nonpolyposis colorectal carcinoma. *Dis Colon Rectum*. 1999;42(6):717–21.
7. Pinol V, Andreu M, Castells A, Paya A, Bessa X, Jover R. Synchronous colorectal neoplasms in patients with colorectal cancer: predisposing individual and familial factors. *Dis Colon Rectum*. 2004;47(7):1192–200.
8. Oya M, Takahashi S, Okuyama T, Yamaguchi M, Ueda Y. Synchronous colorectal carcinoma: clinico-pathological features and prognosis. *Jpn J Clin Oncol*. 2003;33(1):38–43.
9. Luchtefeld MA, Ross DS, Zander JD, Folse JR. Late development of metachronous colorectal cancer. *Dis Colon Rectum*. 1987;30(3):180–4.
10. McFall MR, Woods WG, Miles WF. Colonoscopic surveillance after curative colorectal resection: results of an empirical surveillance programme. *Colorectal Dis*. 2003;5(3):233–40.
11. Passman MA, Pommier RF, Vetto JT. Synchronous colon primaries have the same prognosis as solitary colon cancers. *Dis Colon Rectum*. 1996; 39(3):329–4.
12. Chen HS, Sheen-Chen SM. Synchronous and "early" metachronous colorectal adenocarcinoma: analysis of prognosis and current trends. *Dis Colon Rectum*. 2000;43(8):1093–9.
13. Adloff M, Arnaud JP, Bergamaschi R, Schloegel M. Synchronous carcinoma of the colon and rectum: prognostic and therapeutic implications. *Am J Surg*. 1989;157(3):299–302.
14. McArdle CS, McMillan DC, Hole DJ. Male gender adversely affects survival following surgery for colorectal cancer. *Br J Surg*. 2003;90(6):711–5.
15. Wichmann MW, Muller C, Hornung HM, Lau-Werner U, Schildberg FW. Gender differences in long-term survival of patients with colorectal cancer. *Br J Surg*. 2001;88(8):1092–8.
16. UICC/AJCC. TNM Classification of Malignant Tumors, fifth edition (1997). Wiley-Liss, NY, 1997.
17. Devitt JE, Roth-Moyo LA, Brown FN. The significance of multiple adenocarcinomas of the colon and rectum. *Ann Surg*. 1969;169(3):364–7.
18. Rennert G, Robinson E, Rennert HS, Neugut AI. Clinical characteristics of metachronous colorectal tumors. *Int J Cancer*. 1995;60(6):743–7.
19. Enker WE, Dragacevic S. Multiple carcinomas of the large bowel: a natural experiment in etiology and pathogenesis. *Ann Surg*. 1978;187(1):8–11.
20. Wang HZ, Huang XF, Wang Y, Ji JF, Gu J. Clinical features, diagnosis, treatment and prognosis of multiple primary colorectal carcinoma. *World J Gastroenterol*. 2004;10(14):2136–9.
21. Jass JR. Colorectal cancer. a multipathway disease. *Crit Rev Oncog*. 2006; 12(3–4):273–87.
22. Jass JR. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. *Histopathology*. 2007;50(1):113–30.
23. Masubuchi S, Konishi F, Togashi K, et al. The significance of microsatellite instability in predicting the development of metachronous multiple colorectal carcinomas in patients with nonfamilial colorectal carcinoma. *Cancer*. 1999;85(9):1917–24.

24. Pedroni M, Tamassia MG, Percesepe A, et al. Microsatellite instability in multiple colorectal tumors. *Int J Cancer*. 1999;81(1):1–5.
25. Ueda E, Watanabe T, Umetani N, Ishigami H, Sasaki S, Nagawa H. Microsatellite instability of cancers and concomitant adenomas in synchronous multiple colorectal cancer patients. *J Exp Clin Cancer Res*. 2002;21(2): 149–54.
26. Odin E, Wettergren Y, Nilsson S, et al. Altered gene expression of folate enzymes in adjacent mucosa is associated with outcome of colorectal cancer patients. *Clin Cancer Res*. 2003;9(16 Pt 1):6012–9.
27. Wettergren Y, Odin E, Nilsson S, Carlsson G, Gustavsson B. p16INK4a gene promoter hypermethylation in mucosa as a prognostic factor for patients with colorectal cancer. *Mol Med*. 2008;14(7–8):412–21.