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Determinants of short- and long-term survival from colorectal cancer in very elderly patients

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ABSTRACT

Purpose: Over 5100 colorectal cancers (CRCs) are diagnosed in the United Kingdom in 85 years and older age group per year but little is known of cancer progression in this group. We assessed clinical, pathological and molecular features of CRC with early and late mortality in such patients.

Methods: Data were analysed in relation to early mortality and long-term survival in 90 consecutive patients with CRC aged 85 years or older in a single hospital.

Results: Patients not undergoing operation, those with an ASA score of III or greater and those with advanced tumour stage were more likely to die within 30 days. Regression analysis showed that 30 day mortality was independently related to failure to undergo resection (odds ratio (O.R.), 10.0; 95% confidence interval [C.I.], 1.7–58.2; $p = 0.01$) and an ASA score of III or greater (O.R. 13.0; 95% C.I., 1.4–12.6; $p = 0.03$). All cause three and five year survival were 47% and 23% respectively for patients who are alive 30 days after diagnosis. Three and five year relative survivals were 64% and 54%, respectively. Long-term outcome was independently related to tumour stage (relative risk [R.R.], 2; 95% C.I., 1.3–3.1; $p = 0.001$), presence of co-morbid diseases (R.R., 2.8; 95% C.I., 1.3–6.0; $p = 0.007$) and lipid peroxidation status (R.R., 2.9; 95% C.I., 1.1–7.5; $p = 0.025$).

Conclusions: An active multidisciplinary approach to the care of patients with CRC at the upper extreme of life is reasonable. It also seems sensible to individualise care based upon the extent of disease at diagnosis and the presence of co-morbid conditions. Further studies to examine the role of lipid peroxidation are warranted.

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1. Introduction

The age 85 years and older United Kingdom population increased from 875,000 in 1991 to 1.3 million in 2006 and this population is projected to increase to 3.1 million by 2032.¹ These trends are mirrored by European statistics. Life

expectancy is rising in the Western World and the average survival for 85 year-old males and females in the United Kingdom is now 5.8 and 6.6 years respectively and for 85 year-old Irish males and females it is 5.2 and 6.3 years.² Ageing is a major risk factor for colorectal cancer and United Kingdom incidence rates per 100,000 in men rise from 24

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cases per year at 45 years to 257 per year at 65 years and to 499 per year at 85 years³ with over 5100 CRC currently being diagnosed in the United Kingdom in 85 years and older age group per year.

CRC is a model of a life-threatening but potentially curable disease and very elderly patients are interesting from both a clinical and scientific perspective. From a clinical viewpoint, care strategies are frequently based on trials from which older patients have been specifically excluded.⁴⁻⁶ Furthermore, elderly patients have, in many studies, failed to receive effective treatments based on the unfounded assumption that cancer is relatively benign in this age group, reluctance on the part of the primary provider to refer to a specialist centre, reluctance on the part of the patient,⁷ fear of possible toxicity, and that intensive therapy has little impact on the quality or quantity of remaining life.⁸⁻¹¹ Since 2000, the recruitment of older patients into chemotherapy clinical trials has increased¹² however there are no specific guidelines to direct diagnostic and therapeutic interventions in very elderly patients. The treatment of those at the upper extreme of life often presents significant clinical dilemmas. Considerable health care resources are expended on this disease and to improve CRC survival in the elderly, a critical reappraisal is needed of costs and benefits of treatments, and better selection of patients who can benefit from available therapies is warranted.

As suggested by Gundrum et al., if current trends continue into 2030, 25% of cancer deaths may be in the over 85 years old age group, making it the most vulnerable group.¹³ Thus it is imperative that we conduct biomarker studies to study this cohort of patients and assess the disease similarities and differences in the disease processes versus their younger counterparts.

From a scientific perspective, the specific phenotypic and genotypic characteristics of cancer in very elderly patients are poorly understood. Ageing is generally thought to be associated with accumulation of damage in DNA, proteins and lipids and is also characterised by an increase in intracellular oxidative stress coupled with the production of free radicals.¹⁴ This oxidative stress may be a predisposing factor for a number of age related disorders including atherosclerosis, chronic inflammatory disorders and cancer.^{15,16} Oxidative stress results in the accumulation of a pro-mutagenic lesion, 8-dihydro-2'-deoxyguanine (8-oxo-dG), possibly related to defective DNA repair mechanisms.¹⁷ Studies have demonstrated an increase of 8-oxodG levels with age from muscle DNA¹⁸ and leucocyte DNA¹⁹ from two cohorts of healthy individuals. Noren et al. showed serum levels of 8-oxodG increase with age in a cohort of middle aged women.²⁰ Our group has previously demonstrated that nuclear oxidative damage (8-oxo-dG) is associated with poor survival in CRC across the age spectrum.²¹

Oxidative stress is also associated with lipid peroxidation and the formation of cytotoxic aldehydes including 4-hydroxy-2-nonenal (4-HNE), a mutagen that is thought to play a role in carcinogenesis.²² High levels of 4-HNE is known to have an inhibitory effect on DNA repair and can impair p53 protein function through inhibition of thioredoxin reductase, a protein that governs normal p53 conformation and function²³⁻²⁵ 4-HNE is considered to be the most toxic product

of lipid peroxidation. 4-HNE has been implicated in the tissue damage associated with ageing and other pathological states such as cancer, Alzheimer's, diabetes, cardiovascular and inflammatory complications.²⁶

The variable prognosis of CRC in elderly patients is also of scientific interest as it may allow translational researchers to focus on identifying environmental, patient, tumour and therapeutic factors that might be modified to improve outcomes in the very elderly.

Prior clinical studies have compared survival between very elderly and younger patients with colorectal cancer and showed higher rates of right sided tumours and females in the very elderly.²⁷ Post-operative pulmonary complications have been shown to be higher in the elderly²⁸ however long term relative survival rates were similar when compared to younger patients. Studies have determined that surgical treatment should not be withheld for chronological age only.²⁷⁻²⁹ However, there has been little focus on those clinical, pathological or molecular features of colorectal cancer that might affect mortality at the upper extremity of life, or on potential mortality interactions between cancer and other diseases in this age group. We assessed such variables in 85 year old and older patients with CRC to identify those associated with early mortality and eventual clinical progression.

2. Methods

2.1. Patient population

We studied 90 consecutive patients aged 85 years or older (mean age 87.7 years, range 85.0-93.9) diagnosed with CRC in a single university teaching hospital between 1984 and 2005 (Table 1). All patients with colorectal cancer, are empirically treated according to an accelerated perioperative care package³⁰ that includes preoperative carbohydrate loading, avoidance of bowel preparation, early postoperative mobilisation and

Table 1 – Clinical and pathological factors in 90 patients with colorectal cancer age 85 years and older.

Variable	N = 90
Gender	
Male	31 (24%)
Female	59 (66%)
Surgery	
No	8 (9%)
Yes	82 (91%)
Primary tumour resection	
No	4 (44%)
Yes	5 (56%)
Tumour stage	
Stage I	8 (9%)
Stage II	38 (42%)
Stage III	15 (17%)
Stage IV	29 (32%)
Chemotherapy	
No	90 (100%)
Yes	0 (0%)
Radiotherapy	
No	85 (94%)
Yes	5 (6%)

initiation of feeding, minimal use of drains, nasogastric tubes and opiates and maximum use of laparoscopic surgery, and endotherapy (which appears to be safe and effective in the elderly)³¹ where indicated. In addition, these patients are assessed at a multidisciplinary team conference where treatment options are discussed and perioperative care is planned. Clinical and pathological data were retrieved from a prospective computerised database containing details on all patients with CRC. Furthermore, we retrieved and reviewed charts for all patients to confirm database details. Patients were followed-up to 2008 or until death, using data from out-patient clinic visits, primary care physicians and death certificates held by the National Cancer Registry, Ireland.

We used the American Society of Anesthesiologists (ASA) score to assess physical status at the time of surgery, or at diagnosis for those not undergoing surgery. We also calculated a co-morbidity score based on the presence or absence of specific disease states previously found to be associated with long-term outcome in colorectal cancer.³² Diseases included congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, atrial fibrillation, cerebrovascular disease, dementia, chronic renal failure, peripheral vascular disease, liver disease, hip fracture, paralysis and venous thromboembolism. Finally, we calculated a functional score for each elderly patient based on the presence of impaired mobility, urinary or faecal incontinence or dependence on others to perform activities of daily living.

We retrieved formalin fixed paraffin embedded tumour specimens for 62 patients and constructed tissue microarrays using previously described methods.²¹ Immunohistochemistry was performed to assess expression of the mismatch repair proteins hMLH1 and MSH2, and nuclear and mitochondrial 8-oxo-dG levels were assessed as previously described by us.^{21,33} In addition, we assessed the levels of nuclear and cytoplasmic 4-HNE (Genox Corp, Baltimore, MD) in 62 elderly patients using the same immunohistochemistry protocol. Two independent observers assessed all 8-oxo-dG and 4-HNE staining in a blinded fashion for cellular localisation, percent positivity and intensity (Fig. 1). Approval for this study was obtained from the St Vincent's University Hospital Ethics Committee.

2.2. Statistical Analysis

Continuous data are presented as medians and interquartile ranges and were assessed using the Mann-Whitney U-test. Differences between proportions were assessed using the Chi-square test or Fisher's exact test and multivariate analyses using binary logistic regression analysis. Distributions of 8-oxo-dG and 4-HNE staining were divided around the median value where it is possible in order to develop usable groups to determine the effect of staining on survival in patients aged 85 years and older. The resulting groups contained different numbers of patients, but were as close to equal as it was possible to achieve. Kaplan-Meier survival curves were constructed with overall (all cause) survival or relative survival as end-points. Survival differences were assessed using the logrank test or Cox's proportional hazards model as appropriate using the Statistical Package for the Social Sciences (SPSS, Chicago, IL). Two sided p-values less than 0.05 were considered significant in all analyses.

Overall survival was defined as survival from the point of diagnosis of CRC. Relative survival was defined as the ratio of the proportion of observed cancer survivors to the proportion of expected survivors in the general population, adjusting for gender, age, and date at which the age was coded. Estimates of relative survival were calculated using the Ederer II method.³⁴ This approach compares observed with expected survival at successive follow-up intervals to calculate interval-specific relative survival, then derives cumulative relative survival as the product of successive interval-specific relative survival estimates. Generalised linear modelling of relative survival was performed using Stata version 9.0 (StataCorp, Texas), applying standard generalised linear models to the excess hazard experienced by patients in comparison to the general population.³⁵

3. Results

Twenty-seven patients (30%) had rectal cancer, 25 (28%) had left sided colonic cancer and 38 (42%) had right sided disease. Eighty-two (91%) underwent operation and 77 (86%) primary tumour resection. Five patients (6%) received radiotherapy but no patient received chemotherapy. Nine elderly patients (10%) died within 30 days of diagnosis or surgery, 15 (17%) within 60 days and 17 (19%) within 90 days. Factors associated with 30 day mortality are shown in Table 2. Patients who did not undergo operation, those with an ASA score of III or greater and those with advanced tumour stage (stage IV) at diagnosis were more likely to die within 30 days. Regression analysis showed that 30 day mortality in elderly patients was independently related to no resection performed (odds ratio (O.R.), 10.0; 95% confidence interval [C.I.], 1.7–58.2; $p = 0.01$) and an ASA score of III or greater (O.R. 13.0; 95% C.I., 1.4–123.6; $p = 0.03$).

Subsequent overall three year and five year survivals were 47% and 23% respectively for the 81 patients 85 years and older who were alive 30 days after diagnosis or surgery. Three and five year relative survivals were 64% and 54%, respectively. Long-term overall survival was most strongly related to tumour stage, but the presence of significant co-morbidity and patient gender were also associated with an eventual outcome (Table 3, Fig. 2). Neither microsatellite instability status nor 8-oxo-dG staining was associated with the outcome, but the small number with epithelial nuclear and stromal cytoplasmic 4-HNE staining tended to have a poor prognosis. Regression analysis identified only the tumour stage (relative risk [R.R.], 2.0; 95% C.I., 1.3–3.1; $p = 0.001$), the presence of unrelated co-morbid diseases (R.R., 2.8; 95% C.I., 1.3–6; $p = 0.007$) and stromal cytoplasmic 4-HNE staining (R.R., 2.9; 95% C.I., 1.1–7.5; $p = 0.025$) to be independently associated with long-term outcome (Table 4).

4. Discussion

The age 85 and older population is rapidly rising in the Western World. As a consequence, the growing burden of social and health expenditure of cancer in the elderly is and will become a major challenge that health care systems

Fig. 1 – Representative immunohistochemical images of colorectal tumour tissue with the absence (panel A) and presence (panel B) of epithelial mitochondrial (cytoplasmic) 8-oxo-dG staining (at 10× and 60× magnifications). Nuclear 8-oxo-dG staining is also seen in panel B. Panels C and D show the absence and presence of stromal cytoplasmic 4HNE staining respectively (at 10× and 60× magnifications).

of many countries will have to cope with. A lack of comprehensive observational data on cancer in this patient cohort allied to their frequent exclusion from clinical trials leaves clinicians with a weak evidence base to guide decisions. Considerable health care resources are expended on this disease, and judicious alterations in care patterns might result in significant outcome benefits for patients and economic benefits for health care providers.³⁶

Ten percent of patients aged 85 years and older died within 30 days of surgery or diagnosis. Those who did not undergo tumour resection and those with a high ASA score had the highest mortality. The ASA score was not designed to facilitate decision-making regarding surgery, nor would it be feasible to do so in clinical practice. Seven patients with an ASA score of III or more (24%) died within 30 days, however 22 such patients (76%) survived and their ASA score had no

Table 2 – Factors associated with 30 day mortality following diagnosis in 90 patients with colorectal cancer age 85 years and older.

Variable	Dead at 30 days (n = 9)	Alive at 30 days (n = 81)	p value
Age (year) (median [I.Q. range])	87.4 (86.0–89.0)	87.0 (85.9–89.2)	0.50 ^a
Gender			
Male	3 (33%)	28 (35%)	1.0 ^b
Female	6 (67%)	53 (65%)	
Primary tumour resection			
No	4 (44%)	9 (11%)	0.02 ^b
Yes	5 (56%)	72 (89%)	
Tumour stage			
Stage I	0	8 (10%)	0.003 ^c
Stage II	1 (11%)	36 (46%)	
Stage III	1 (11%)	14 (17%)	
Stage IV	7 (78%)	22 (27%)	
ASA score ^d			
ASA I–II	1 (13%)	48 (62%)	0.009 ^b
ASA III–V	7 (8%)	29 (38%)	
Co-morbidity scores ^e			
Score = 0	2 (25%)	37 (47%)	0.29 ^b
Score ≥ 1	6 (75%)	42 (53%)	
Functional disability score ^f			
Score = 0	3 (33%)	46 (58%)	0.18 ^b
Score ≥ 1	6 (66%)	33 (42%)	

Because of rounding, percentages do not always total 100.

^a Mann–Whitney *U*-test.

^b Fisher's exact test.

^c Chi square test for trend.

^d ASA score was not documented in 5 cases.

^e Co-morbidity score was unavailable for three patients.

^f Functional disability score was unavailable for two patients.

influence on long-term outcome. The increased postoperative mortality in patients with a high ASA score suggests that further emphasis should be placed on maximising performance status after treatment options and possible outcomes have been discussed with patients and their family.

Our study showed females exhibiting a survival advantage. Previous studies have demonstrated a gender difference in survival with younger females exhibiting better survival rates partially explained by the favourable effect of endogenous female sex hormones.^{37,38} However these studies showed an opposite pattern in older female patients who exhibited lower survival rates. A recent study demonstrated a survival advantage in women up to the age of 64³⁹; however, to our knowledge this is the first study to show a difference in survival between the sexes in the very elderly.

Multimorbidity is highly prevalent in the elderly population and has been shown to be associated with reduced survival in CRC in previous studies.^{32,40} This study re-iterated the impact of the presence of significant co-morbidity has on survival outcome, a co-morbidity score greater than one was independently associated with poor survival. It is likely that multi-morbidity affects survival outcome on several levels. Firstly, the presence of co-morbid conditions has a negative association with the receipt of standard cancer treatment.⁴¹ However it is likely that multimorbidity could affect the

Table 3 – Clinical, pathological and molecular factors associated with long-term survival in 81 patients with colorectal cancer age 85 years and older who were alive 30 days after diagnosis.

Variable	Number	Three year survival	p value
Gender			
Male	28	34%	0.04 ^a
Female	53	53%	
ASA score ^b			
ASA I–II	48	46%	0.70 ^a
ASA III–V	29	50%	
Co-morbidity score ^b			
Score = 0	37	63%	0.002 ^a
Score ≥ 1	42	35%	
Functional disability ^b			
Score = 0	46	52%	0.71 ^a
Score ≥ 1	33	43%	
Tumour stage			
Stage I	8	50%	0.0001 ^a
Stage II	37	69%	
Stage III	14	32%	
Stage IV	22	21%	
Microsatellite instability status			
Stable	7	43%	0.82 ^a
Unstable	55	54%	
Epithelial nuclear 8-oxo-dG ^c			
Low	30	54%	0.15 ^a
High	29	52%	
Epithelial cytoplasmic 8-oxo-dG ^c			
Low	27	49%	0.92 ^a
High	32	57%	
Stromal nuclear 8-oxo-dG ^c			
Low	24	60%	0.98 ^a
High	32	48%	
Epithelial nuclear 4-HNE ^d			
Absent	55	58%	0.003 ^a
Present	7	14%	
Epithelial cytoplasmic 4-HNE ^c			
Low	29	59%	0.07 ^a
High	33	47%	
Stromal cytoplasmic 4-HNE ^d			
Absent	54	59%	0.006 ^a
Present	7	14%	

^a Logrank test.

^b Data were not available for all cases.

^c Cutoff at median value.

^d Positive 4-HNE staining in only 7 cases.

outcome independent of anti-cancer therapy, for example diabetes, renal failure, atherosclerosis and chronic obstructive pulmonary disease (COPD) are all are known to be associated with high levels of oxidative stress, could this higher level of oxidative stress be leading to a more aggressive tumour phenotype.

Surprisingly 21% of patients with stage IV cancer were alive at 3 years, despite not receiving chemotherapy. This highlights again the possibility that CRC in the very elderly cannot be deemed the same disease as in the younger counterparts. Furthermore, a recent study from The Netherlands showed that elderly patients with breast cancer have a higher risk not just for under-treatment but are also at risk for overtreatment and there exists a delicate balance between potential

Fig. 2 – Survival of 81 patients with colorectal cancer, age 85 years and older, who were alive 30 days after diagnosis. 4-HNE expression refers to stromal cytoplasmic 4-HNE staining.

toxicities of treatment and survival gain.⁴² The number of elderly patients with CRC is increasing and will contribute to the strain on health resources. However, little is known about the optimal treatment for this age group. To improve CRC survival in the elderly, a critical reappraisal is needed for the cost and benefits of treatments, and a better selection of patients who can benefit from available therapies is warranted.

As part of our study, we assessed molecular factors that have been thought to be associated with ageing and which have also been implicated in cancer formation. The ageing process is associated with accumulation of mitochondrial DNA damage and increased mitochondrial oxidative stress. 8-oxo-dG staining was not associated with long-term outcome in these elderly patients in contrast to a previous study of a younger CRC group

in which 8-oxo-dG staining was associated with poor outcome.²¹ If one considers the differences that have been noted in CRC presenting in the very young (<40 years old) for example a higher prevalence of mucinous or poorly differentiated tumours including signet ring tumours which carry a poorer prognosis,^{43,44} it is not unreasonable to consider that CRC in the very elderly carries a different phenotype from the average CRC age group also, and that other factors may play a more important role in the pathogenesis and survival. The fact that the very elderly group have avoided cancer to this late age may represent a “healthier” lifestyle and it has been shown that both caloric restriction and moderate exercise lead to lower accumulation of both nuclear and mitochondrial 8-oxo-dG in both rat and human models.^{45,46} A recent study has suggested that diet, lifestyle, and genetic factors contribute to colorectal tumorigenesis through their influence on oxidative stress. It suggests that those with an inherited genetic profile placing them at higher risk for oxidative stress can reduce their colon and rectal cancer risk by diet and lifestyle factors.⁴⁷

In contrast to nuclear and mitochondrial 8-oxo-dG levels, both epithelial and stromal 4-HNE staining strongly correlated with a poor outcome. Stromal cytoplasmic 4-HNE was associated with survival independent of both tumour stage and co-morbid conditions. 4-HNE is a by-product of lipid peroxidation which occurs as a consequence of oxidative stress in the mitochondria. During LPO, a variety of ROS and reactive nitrogen species (RNS) oxidize lipids leading to free radical chain reactions and subsequent formation of byproducts, like lipid radicals, hydrocarbons and aldehydes,^{48,24} 4-HNE is an example of one such aldehyde. A number of recent studies have demonstrated not only an age-association of lipid peroxidation, but also an increase of lipid peroxidation in several age-related diseases, such as Alzheimer's^{49,50} and also in obesity and the metabolic syndrome⁵¹. These α,β -unsaturated aldehydes are diffusible, can covalently modify proteins, and are known to form mutagenic DNA adducts⁵²⁻⁵⁴. Amongst these, 4-HNE has been the most intensively studied and may additionally contribute to carcinogenesis by inhibiting DNA repair,²⁵ inducing cyclooxygenase-2 and modulating mitogen-activated protein kinase and nuclear factor κ B signalling.⁵⁵⁻⁵⁷ Wang et al. demonstrated that 4-HNE purified from enterococcus faecalis infected macrophages induced G2-M cell cycle arrest, leading to formation of H2AX foci, and disrupted the mitotic spindle in both normal colonic epithelial and colon cancer cell lines.⁵⁸ This study suggested the role of 4-HNE as a mediator of the bystander effects by the superoxide producing enterococcus faecalis.⁵⁸ High levels of 4HNE have previously been noted in CRC tissue versus normal matched control⁵⁹ however this is the first study that shows HNE levels to be associated with outcome in CRC in the elderly population. Our molecular results may point to subtle differences in the genesis of CRC at the upper extreme of life and further integration of clinical and laboratory research strands may provide additional insights into cancer initiation and progression in this very elderly patient group.

Our study is original insofar as it integrates clinical details, including pre-morbid disease states and functional status, with pathological results, molecular data, postoperative outcome and long-term survival in very elderly patients with colorectal cancer. A previous large population-based study, found that the decrease of cancer survival rates with increasing

Table 4 – Final Cox regression model identifying factors associated with overall long-term survival in 81 patients with CRC age 85 years and older who were alive 30 days after diagnosis.

Variable	Beta	Odds ratio (95% C.I.)	p value
Tumour stage	0.7	2.0 (1.3–3.1)	0.001
Co-morbidity score	1.05	2.8 (1.3–6.0)	0.007
Stromal cytoplasmic 4-HNE ^a	1.08	2.9 (1.1–7.5)	0.025

^a Positive 4-HNE staining in only 7 cases.

age at diagnosis was more marked in Europe and that elderly American patients had better prognosis than their European counterparts. This was felt to be secondary to earlier disease stage at diagnosis and more aggressive treatments regardless of age in the US.⁶⁰ As a consequence of the relative survival rate results, we suggest that it is indeed reasonable to take an active multidisciplinary approach to the care of patients at the upper extreme of life and support a view that we should individualise care based upon the extent of disease at diagnosis, co-morbid conditions and the “biological” age rather than the “chronological” age.

Disclosures and Conflict of Interest Statements

No author has any conflict of interest or financial interest in this manuscript.

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