Gastrointestinal Cancer: Research & Therapy

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Austin Publishing Group

Research Article

Colorectal Cancer; the Trend towards Earlier Age of Presentation

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Received: November 29, 2017; **Accepted:** January 02, 2018; **Published:** January 09, 2018

Abstract

Background: Colorectal cancer (CRC) is the second leading cause of cancer related death in the UK. 55-64 year olds in England are eligible for 'bowel scope' screening within the NHS since 2016. Literature has indicated a rising incidence of CRC below the age of 40 years.

Aims: To assess the incidence of CRC in the under 55-year age group, in the South East of England over the past 10 years. Secondary outcome measures include comparative survival rates and right versus left sided cancer rates.

Designs and Setting: A retrospective analysis of 3472 CRC patients at a single institution from January 2005 to January 2016 was performed.

Methods: Local electronic cancer registry databases, histopathology databases and electronic patient records were used.

Results: The incidence for under 55 year olds with CRC has increased over the last 10 years, in 2005 6.6% of patients versus 13.1% in 2015, (R^2=80.18%), median survival was greater than 10 years in the under 55 years age group. The overall age distribution has reduced, the mean age of the patients between 2005-7 has decreased from 73 years of age to 70.5 years of age over the last 5 years ($P<0.001$). This study has shown no significant cancer survival rates in left versus right sided disease.

Conclusions: This study has important implications with regards to screening and early referral. With an increasing incidence of CRC in patients below the age of screening, measures need to be taken to capture this cohort of patients earlier, with changes to referral practice and early investigation in primary health care.

Keywords: Colorectal cancer; Survival; Age; Primary health care; Referral

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer related death in the UK. According to the office of national statistics in 2013, CRC is the eighth leading cause of death in 35-49 year olds and the fourth in 50-64 year olds. 11% of Colon and 18% of rectal cancers occur in patients below the age of 50 years [1].

Risk stratification, lifestyle modification, early screening and prophylactic surgery are helpful in patients with hereditary components to their disease. However little is available to diagnose the younger patient without a known predisposition to CRC [2,3]. Literature has indicated that the incidence of CRC has been rising in people below the age of 40 years [1,4-6].

Since the 1990s Bowel cancer incidence in the UK has increased for most age groups, but it has remained stable in people aged between 50-59 and 60-69. The largest increase in incidence has been in people aged between 25-49 [1,4,7-11]. European age specific incidence rates increased by 34% between 1993-1995 and 2012-2014 [1].

CRC has been considered an older age disease often leading to delayed screening and referrals in younger patients with colonic symptoms [2,3,8,10-13]. Average risk screening is now recommended in the United Kingdom to commence after the age of 55 years old, data had shown that there is an increasing trend towards younger patients developing CRC. This study aims to confirm whether this trend is reflected in local population and establish whether younger patients are presenting with more aggressive tumours.

It is well established that poorly differentiated histological features such as mucinous and signet ring features are common in younger patients and associated with a poorer prognosis in CRC [8-15]. The increasing incidence is a younger working population will have significant impact on risk stratification and screening as well as a change in the traditional mind-set that CRC is a disease of the elderly [11,13,14].

CRC is a heterogeneous disease and better understanding its biology eventuates targeted therapy with improved survival and prognosis. CRC biomarkers that have been extensively evaluated include KRAS, NRAS and BRAF mutations, DNA mismatch repair status, microsatellite instability and CpG island methylation [14]. The mutational status of KRAS and NRAS is indicative of a worse prognosis and predicts for lack of efficacy of anti-epidermal growth factor receptor (anti-EGFR) antibody therapy [6]. It has been found that 8-10% of CRC patients have BRAF mutations [14-16]. Multiple

Citation: Cunin L, Balakumar C, Wall J, Chambers D and Hill M. Colorectal Cancer; the Trend towards Earlier Age of Presentation. Gastrointest Cancer Res Ther. 2018; 3(1): 1026.

studies have shown that mutation in BRAF have a more aggressive disease and worse outcome in the metastatic setting. Recently it has been demonstrated that right sided tumours offer a worse prognosis in the metastatic setting, and that right and left sided tumours have a different molecular profile [12,14,16-20]. Furthermore, right sided tumours are less likely to respond to anti-EGFR therapy.

Methods

The aim of this study in a single institution was to assess whether there is an increasing incidence in CRC in patients under the age of 55 and whether they present with more aggressive disease. Primary outcome measures were rates of CRC in the under 55 year olds versus over 55 year olds and rates of survival. Secondary outcome measures were sidedness and molecular profiles.

A retrospective analysis of all patients diagnosed with colorectal cancer in a single institution between January 2005 to December 2015. 3472, CRC patients were assessed using the local electronic cancer registry database, the hospital trust information and coding department and the local histopathology database.

Patients were grouped into age categories below age 55 and above, consistent with the recommended age of screening via the 'Bowel Scope' programme.

Sidedness data and survival data was accessible from 2009, therefore 2,992 patients were analysed, and 432 patients were excluded due to either incomplete electronic hospital records, pathology reports or oncological records.

Statistical analysis was performed using linear regression (R^2 calculations), Kaplan Meier analysis and all statistical tests were two-tailed ($p<0.05$). Statistical analyses were performed using XLSTAT statistical software.

Results

The number of patients presenting with CRC under the age of 55years of age has been increasing with a trend as indicated on Figure 1 (R^2= 0.8). The overall incidence of CRC is increasing in all age groups as highlighted in this cohort (Figure 2).

The age distribution has also been demonstrated to be shifted to the left, as compared with Holt et al who showed a distribution curve with a peak incidence of approximately 90 years of age, the peak incidence in this study suggests a peak incidence in the 70th decade (Figure 3). The mean average age of the incidence CRC in patients in this study decreases from 72-73 yrs between 2005-7 to 70-71 from 2011-2015, ($P<0.001$).

Survival analysis of the 2,992 is demonstrated in Figure 4. Median survival was greater than 10 years whilst in the over 55 year age group median survival was 7 years post diagnosis. It can be seen that there is approximately 75% 5-year survival in the under 55-year age group (Figure 5).

Sidedness survival analysis for all age groups does not show a significant difference in survival in this cohort (Figure 6). Survival rates were found to be higher in both left and right sided disease in the under 55-year age group as compared with the over 55-year age group.

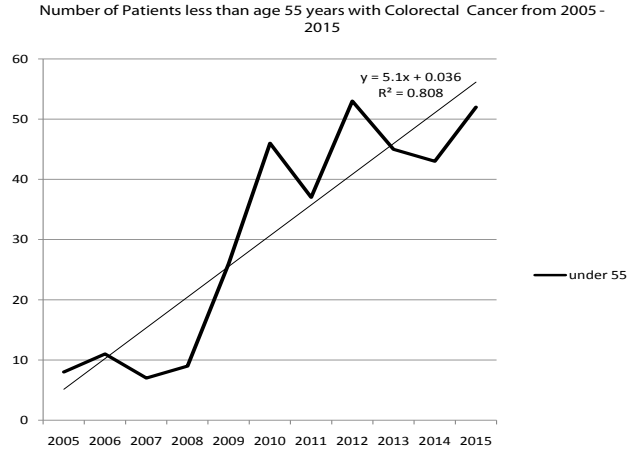

Figure 1:

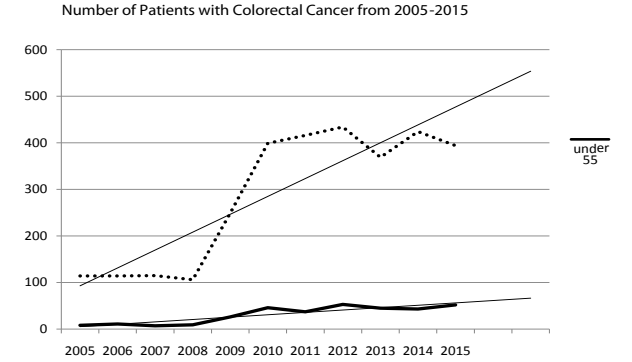

Figure 2:

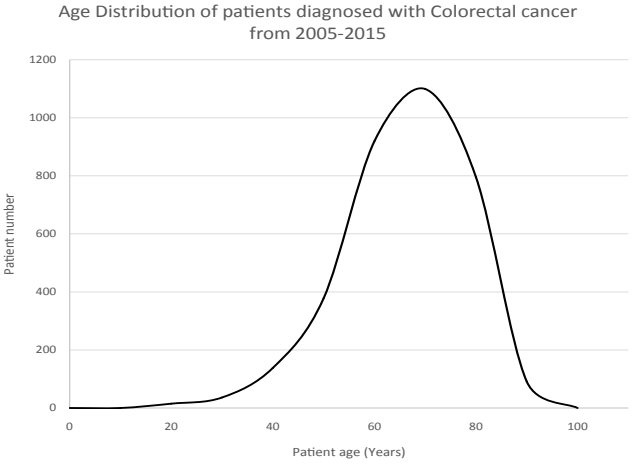

Figure 3:

Data analysis for molecular profiling data has been limited due to small numbers and a limited time frame due to changes in trust data collection and accessibility and the commencement of internal molecular analysis (Appendix 1).

Discussion and Conclusion

This study confirms the fact that there is an increasing incidence

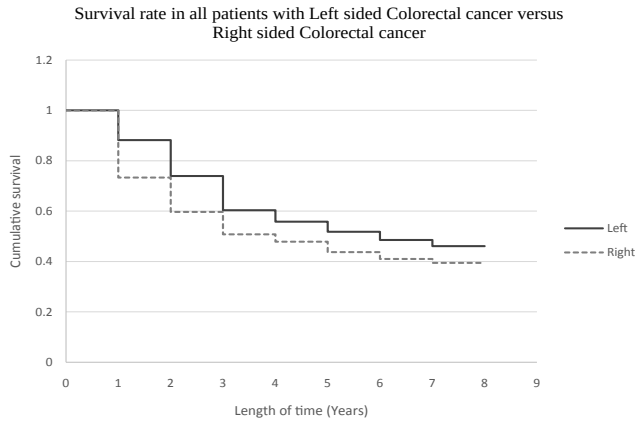

Figure 4:

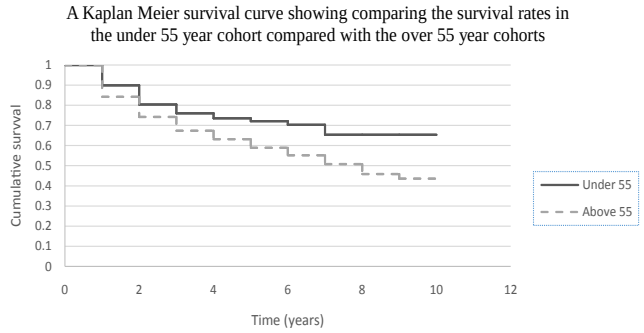

Figure 5:

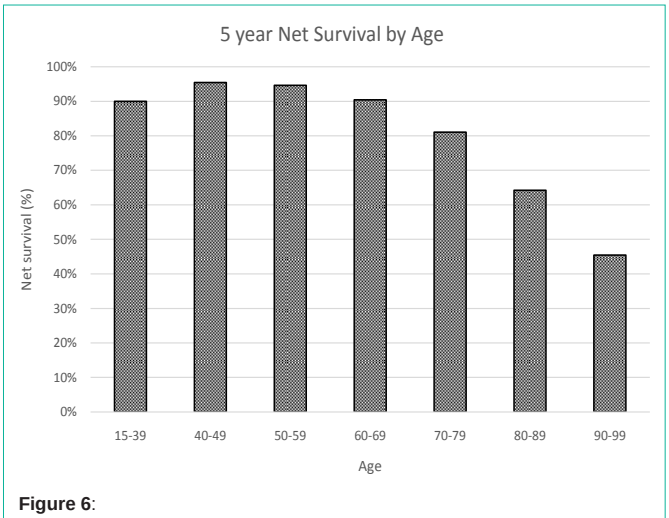

Figure 6:

of CRC in the younger patient, below the age of 55-years; this has important implications for clinical practice. Certainly in the United Kingdom this age group would not be screened and delays to referrals often lead to delayed and more advanced presentations of disease.

Reassuringly however, in this study survival rates were better than the older age group whereby median survival is greater than 10 years. Linear regression has suggested that there is an upward trend to incidence in this younger cohort and therefore this cohort needs to be targeted to improve early diagnosis and subsequent prognosis. The survival advantage of being a younger (<55 years) patient can be relayed to patients from this study enabling counselling during diagnosis with median survival being greater than 10 years. However, survival was calculated based on all deaths over 10 years not just cancer related deaths, and therefore improved survival maybe in part, due to simply being younger and having a lower disease burden than an older population.

75% 5-year survival in the under 55-year age group is reassuring however, it cannot be understated that in this very young patient cohort 25% are dying within 5 years which is a large group in an essentially young healthy population where we do not expect high rates of mortality. Holt et al showed an age distribution curve with incidence of CRC peaking at approximately 90 years of age (from 1999-2003) but our study shows a peak incidence at approximately 72 years of age (2005-2015), this is a rapid increase in incidence in the younger age group and will have a large socioeconomic impact as the rates of CRC are affecting the working population more. The rapid increase in the incidence of CRC in increasingly younger patients will lead to a considerable burden on modern healthcare systems, have a negative effect on economic growth and highlights the need for research into causative factors and preventative medicine. Causative factors may include lifestyle factors, with surrogate measures to include BMI, diet and socioeconomic status.

Sidedness survival analysis for all age groups did not show a significant difference in survival however literature has been shown to confer a survival advantage in the metastatic setting, analysis in this cohort was for all groups [12,18-20].

Unfortunately, limitations to the molecular profiling has meant that a molecular analysis on has been very limited and should be a primary outcome measure in another study. Therefore, we have been unable to answer whether younger patients present with more aggressive disease in this cohort. Higher rates of mutant KRAS BRAF and NRAS were not seen during this study, however analysis was very limited. Differences in tumour biology in the over and under 55-year age groups cannot be assessed.

From this study we propose that certainly within the South East of England there is enough evidence to recommend a support system to enable early referral for younger patients in primary care. With additional support for Family Medicine Practitioners who may traditionally have been advised that CRC is an older age disease. Additionally, an algorithm examination and investigation series in the community preventing a large influx of referral to secondary care may be feasible, given the current resource allocation within the healthcare system. It is apparent that this must become a priority as the cohorts affected more and more will become the working younger population. Certainly current data suggests that even if younger patients do not fit the criteria for early fast track cancer referral pathways they should be referred for endoscopy early.

Further study is required into the molecular profiling of the younger cohort, presently within our institution this is only performed in metastatic disease. However, assessing the histology and biology of the tumours in the age groups above and below the age of 55 years may prove particularly useful in establishing tumour nature and therefore the oncological therapy used.

References

1. Cancer Research UK. Cancer research UK, bowel cancer mortality by age. Bowel Cancer mortality by age Web site. 2017.
2. Dozois EJ, Boardman LA, Suwanthanma W, et al. Young-onset colorectal cancer in patients with no known genetic predisposition: Can we increase early recognition and improve outcome? Medicine (Baltimore). 2008; 87: 259-263.
3. Davis DM, Marcet JE, Frattini JC, Prather AD, Mateka JJ, Nfonsam VN. Is it time to lower the recommended screening age for colorectal cancer? J Am Coll Surg. 2011; 213: 352-361.
4. Fairley TL, Cardinez CJ, Martin J, et al. Colorectal cancer in U.S. adults younger than 50 years of age, 1998-2001. Cancer. 2006; 107: 1153-1161.
5. Ganapathi S, Kumar D, Katsoulas N, et al. Colorectal cancer in the young: Trends, characteristics and outcome. Int J Colorectal Dis. 2011; 26: 927-934.
6. Young JP, Win AK, Rosty C, et al. Rising incidence of early-onset colorectal cancer in australia over two decades: Report and review. J Gastroenterol Hepatol. 2015; 30: 6-13.
7. Ahnen DJ, Wade SW, Jones WF, et al. The increasing incidence of young-onset colorectal cancer: A call to action. Mayo Clin Proc. 2014; 89: 216-224.
8. Hubbard JM, Grothey A. Adolescent and young adult colorectal cancer. J Natl Compr Canc Netw. 2013; 11: 1219-1225.
9. Merrill RM, Anderson AE. Risk-adjusted colon and rectal cancer incidence rates in the United States. Dis Colon Rectum. 2011; 54: 1301-1306.
10. Meyer JE, Narang T, Schnoll-Sussman FH, Pochapin MB, Christos PJ, Sherr DL. Increasing incidence of rectal cancer in patients aged younger than 40 years: An analysis of the surveillance, epidemiology, and end results database. Cancer. 2010; 116: 4354-4359.
11. Varma JR, Sample L. Colorectal cancer in patients aged less than 40 years. J Am Board Fam Pract. 1990; 3: 54-59.
12. Barton MK. Primary tumor location found to impact prognosis and response to therapy in patients with metastatic colorectal cancer. CA Cancer J Clin. 2017; 67: 259-260.
13. Taggarshe D, Rehil N, Sharma S, Flynn JC, Damadi A. Colorectal cancer: Are the "young" being overlooked? Am J Surg. 2013; 205: 312-316; discussion 316.
14. Gryfe R, Kim H, Hsieh ET, et al. Tumor microsatellite instability and clinical outcome in young patients with colorectal cancer. N Engl J Med. 2000; 342: 69-77.
15. O'Connell JB, Maggard MA, Liu JH, Etzioni DA, Livingston EH, Ko CY. Do young colon cancer patients have worse outcomes? World J Surg. 2004; 28: 558-562.
16. Hsu HC, Thiam TK, Lu YJ, et al. Mutations of KRAS/NRAS/BRAF predict cetuximab resistance in metastatic colorectal cancer patients. Oncotarget. 2016; 7: 22257-22270.
17. He WZ, Liao FX, Jiang C, et al. Primary tumor location as a predictive factor for first-line bevacizumab effectiveness in metastatic colorectal cancer patients. J Cancer. 2017; 8: 388-394.
18. Benedix F, Kube R, Meyer F, et al. Comparison of 17,641 patients with right- and left-sided colon cancer: Differences in epidemiology, perioperative course, histology, and survival. Dis Colon Rectum. 2010; 53: 57-64.
19. Arnold D, Lueza B, Douillard JY, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomised trials. Ann Oncol. 2017; 28: 1713-1729.
20. Arora SP, Ketchum NS, Michalek J, Gelfond J, Mahalingam D. Left versus right: Does location matter for refractory metastatic colorectal cancer patients in phase 1 clinical trials? J Gastrointest Cancer. 2017.

Appendix 1

314KRAS tests were performed in total; there were 17 exclusions due to inadequate results and samples. 121KRAS mutations detected 131RAS mutations detected (including NRAS). Of the 176 cases that went forward for BRAF testing, 38 were mutant at V600 (Table 1).

Table 1:

	KRAS	Mutant	Wild type (WT)	Exclusions
Total	314	121 (38.54%)	176 (56.05%)	17 (5.41%)
≤ 50 age group	41	13 (31.71%)	27 (65.85%)	1 (2.44%)
> 50 age group	273	108 (39.56%)	149 (54.58%)	16 (5.86%)
	BRAF	**Mutant**	**WT**	**Exclusions**
Total	176	38 (21.59%)	138 (78.41%)	0
≤ 50 age group	27	5 (18.51%)	22 (81.48%)	0
> 50 age group	149	33 (22.15%)	116 (77.85%)	0
	NRAS	**Mutant**	**WT**	**Exclusions**
Total	176	11(6.25%)	165(93.75%)	0
≤ 50 age group	27	13(7.69%)	26(96.29%)	0
> 50 age group	149	10(6.71%)	139(93.28%)	0

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