Title:

Exclusion of gastrointestinal cancer patients with prior cancer from clinical trials: Is this justified?

Running Title:

Justifiable clinical trials eligibility

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Microabstract

Eligibility criteria for clinical trials are important for maintaining patient safety and scientifically valid results. Patients are commonly excluded from trials due to a history of a previous cancer. We demonstrate that patients with a previous cancer have similar survival to those who do not, and that this is not a justifiable reason to exclude them from clinical trial participation.

Abstract

Background:

Strict eligibility criteria are necessary to maintain patient safety and scientific validity in clinical trials. However this may lead to impaired generalizability of results. As survival in gastrointestinal (GI) cancer relates mainly to the GI malignancy, we hypothesised that previous cancers do not impact on survival and are not a rational exclusion criterion.

Materials and Methods:

Patients treated with chemotherapy for a GI cancer in 2006 were identified from the electronic patient record at the Royal Marsden, London. Chart review was performed and patient age, gender, GI cancer stage, prior cancer stage, clinical trial availability/eligibility, and dates of cancer recurrence, death and last follow up were collated.

Results:

697 patients were identified. 54 patients (8%) had a prior cancer; commonly breast (26%), prostate (17%), or colon (9%); most were stage I (42%) or II (37%). 297 (65%) patients had GI cancer recurrence, 7 (12%) patients had relapse of a prior cancer. 504 (72%) patients have died, 170 (24%) are alive with no cancer and 23 (3%) patients are alive with cancer. 476 (94%) died of GI cancer, 2 (0.3%) of their prior cancer. 489 (70%) of all patients had an available trial but 30% of patients with a prior cancer were ineligible for

this reason. Overall and GI cancer specific survival were comparable for patients with/without a prior cancer.

Conclusions:

Survival for patients with a GI cancer requiring chemotherapy relates to the GI cancer and rarely a prior cancer. These patients should not be excluded from clinical trial participation.

Clinical practice points

What is already known about this subject?

Exclusion of patients from clinical trials due to a previous cancer diagnosis is common however there is limited evidence to support this practice. As rates of cancer survival increase and a large group of patients are excluded from clinical trial participation it is necessary to challenge this paradigm.

What are the new findings?

We demonstrate that for patients with a new diagnosis of a gastrointestinal cancer and a history of a previous cancer that their survival relates to the current gastrointestinal cancer and not their previous malignancy. Furthermore, one third of patients with a previous cancer were prevented from participating in a clinical trial due to their previous cancer.

How might it impact on clinical practice in the foreseeable future?

We conclude that patients with a previous cancer which had been previously treated should not be excluded from clinical trial participation. As survivorship issues become more prevalent it is important that these patients have just access to clinical trials. Clinical trial generalizability is also improved by including patients reflective of the general population.

Introduction

Randomised clinical trials are the backbone upon which novel, increasingly effective therapies for cancer are based, and patient participation in randomised trials may lead to enhanced survival in particular in the short term.[1, 2] However the relevance of any clinical trial relies heavily on external validity and trial generalizability may be significantly affected by factors such as exclusion criteria.[3] Furthermore although results from clinical trials provide the empirical evidence used to treat patients rationally, patient accrual often falls short of expectations. This is demonstrated by a study of 114 Medical Research Council sponsored trials which revealed that less than one-third achieved their target enrolment within the specified timeframe.[4] Such low accrual rates may lead to insufficient statistical power and early trial termination. This represents a missed opportunity to answer a clinical and scientific question and a squandering of scant resources.

In theory, stringent eligibility criteria are necessary for clinical trials in order to maintain the safety of the patient and the scientific value of the protocol. Many of these criteria are common to all clinical trials and along with "poor performance status" one of the most frequent of these is the exclusion of patients with any previous invasive cancer. [5, 6] As the population ages and treatments of early stage tumours improve the proportion of patients with a prior history of cancer will inevitably increase – in 1971 there were 3 **million** cancer survivors in the United States, by 2007 this was 11.7 **million**.[7] Excluding these patients may further decrease the pool of potential clinical trial participants and may limit the generalizability of trials which are performed. Although many suggestions have been made as to how to increase participation in clinical trials, the validity of this commonly used exclusion criteria has not been previously examined.

As survival for patients with advanced gastrointestinal cancers (oesophagogastric (OGJ)], pancreatic, hepatocellular (HCC], cholangiocarcinoma and colorectal cancer) is more likely to be determined by that cancer that any previous cancer we hypothesised that previously treated, unrelated cancers are less likely to impact on survival than is suggested and that therefore a history of a previously treated cancer may not be rational reason to exclude patients from clinical trials in gastrointestinal malignancies.[8-12] In this study, we examine the survival outcomes of patients with and without a prior cancer treated with chemotherapy in the GI Unit of the Royal Marsden Hospital over a one year period, and how a history of a previous cancer in a patient affected clinical trial eligibility during that timeframe.

Materials and Methods

For this retrospective observational study we collected data on patients with gastrointestinal cancer (colorectal, oesophagogastric, pancreatic, and hepatocellular cancer) who received treatment between 1st of January 2006 and 31st of December 2006 at the Royal Marsden Hospital, London. Patient details were extracted from the electronic patient record. Eligibility criteria included age of 18 and over, diagnosis of colorectal, gastro-oesophageal, pancreatic, or hepatocellular cancer and treatment with chemotherapy in the year 2006. The following information was collected following chart review: patient age, gender, gastrointestinal cancer stage, prior cancer tissue of origin and stage, clinical trial availability and eligibility, and dates of cancer recurrence, death, cause of death and last follow-up. The electronic records of the Gastrointestinal Clinical Trials Unit were reviewed to identify the opening and closing dates of pertinent clinical trials for the period under review, and the relevant protocols were reviewed with respect to eligibility criteria.

All non-trial patients in the Gastrointestinal Oncology Unit are followed according to departmental protocols. Patients receiving active treatment for metastatic disease are

followed as per chemotherapy protocol whilst receiving chemotherapy and three monthly whilst on treatment breaks. Patients with resected neoadjuvantly or adjuvantly treated cancers are followed every three months for the first year, then six monthly for years two and three following resection, and then annually until year five when they are discharged. Patients with resected stage IV colorectal cancer are followed for seven years. Survival outcomes are collected by hospital administrative staff from a national database. Patients participating in clinical trials were followed as per individual trial protocol.

Overall survival (OS) was calculated from date of diagnosis of gastrointestinal cancer to date of death and gastrointestinal cancer specific survival (GCSS) was calculated from date of diagnosis of gastrointestinal cancer to date of death where cause of death was GI cancer (censored at date of death for other cause of death). Survival estimates were calculated according to the Kaplan-Meier method, and are presented with 95% confidence intervals. Differences in survival between groups were compared with the log-rank test. All analysis was performed in SPSS version 22. Multivariate Cox regression analysis was performed using the variables age, stage, and cancer subtype in order to assess the independent impact of these variables on gastric cancer specific and overall survival. The study was reviewed and approved by the Institutional Review Board (SE61) and did not require patient consent, nor did it have any influence on patient management. The year 2006 was chosen to allow for adequate follow up of at least 5 years for surviving patients and mature assessment of survival data.

Results

Patient population

A total of 697 patients were identified. Patient characteristics are presented in Table 1. The majority of patients were male (59%), median age was 62 years for all patients. The most commonly treated GI tumour type was colorectal cancer (74%). Fifty-four (8%) of patients had a previously treated cancer. Breast, prostate and colon cancer together

accounted for more than half of these previous cancers; almost 80% of previously treated cancers were Stage I or II. The median time from diagnosis of a previous cancer until current diagnosis was 7.9 years. Patients with a prior cancer were significantly older than patients without (median 61 years vs 67 years, $p<0.001$), but were similar in all other baseline characteristics.

Of the 459 patients in the study with GI cancer that did not have metastatic cancer at presentation, 297 (65%) developed a recurrence of their GI cancer. Of the 54 patients with a previously treated cancer 7 (12%) developed a recurrence of the previously treated cancer (however five of these recurrences had occurred prior to their GI cancer diagnosis and been treated successfully with curative intent). Two patients had a recurrence of a previous cancer after their GI cancer diagnosis. These were one patient with a previous spinal cord glioma and a one patient with a history of resected bladder cancer, and both of these patients died of their recurrent original non-GI cancer. To date, 504 (72%) patients have died, 170 (24%) are alive with no cancer and 23 (3%) patients remain alive with cancer. Among the deceased patients, their primary GI cancer was the cause of death in 476 (94%) patients, followed by other reasons in 26 (5%) of patients and their prior cancer in 2 (<1%) patients**.**

Impact of prior cancer on clinical trial recruitment

Of the 697 patients who were treated in the referent time period, 489 (70%) patients had an available clinical trial at the time of gastrointestinal cancer treatment, and 113 (23% of patients with trial available, 16% of all patients) were enrolled into a clinical trial. Nine (2% of total) patients with a trial available were excluded because of a prior history of cancer. Of the 30 patients with prior cancer for whom a clinical trial was identified, nine of these (30%) patients were excluded due to their previous malignancy**. Thirteen patients were excluded from trial participation for other reasons; of the remainder who were trial**

eligible with an available trial (n=8) 55% chose to participate in a clinical study. Both gastrointestinal cancer specific survival and overall survival were comparable between patients who participated and who did not participate in clinical trials. These were 35.4 months (95% CI 25.4 – 45.5 months) versus 41.5 months (95% CI 34.0 – 49.0 months), HR 1.06 (95% CI 0.82 – 1.37), p= 0.662 for **gastrointestinal cancer specific survival** and 35.4 months (95% CI 25.4 – 45.5 months) versus 40.0 months (95% CU 32.8 – 47.2 months), HR 1.00 (95% CI 0.78 – 1.29), p=0.991 for **median overall survival** respectively.

Impact of prior cancer on survival

Median follow-up time was 83.2 months (95% Cl: 77.9 – 88.5 months). Median gastrointestinal cancer specific survival (GCSS) was 41.4 months (95% CI: 36.7 – 46.1) for all patients. This (GCSS) was 41.2 months (95% CI: 36.1-46.3) for patients with no history of a previous cancer versus 47.4 months (95% CI: 32.8-62.0) for prior cancer patients (p=0.75) **(Fig 1)**. Median overall survival (OS) for all patients was 40.6 months (95% CI: 36.1 - 45.0). This was 40.6 months (95% CI: 36.1-45.1) for patients with no prior cancer patients versus 37.4 months (95% CI: 20.7-54.0) for patients who did have a prior cancer, these were not significantly different (p= 0.42) **(Fig 2)**. Survival was comparable for patients with curatively resected cancer (Stage I-III) and for patients with advanced disease (Stage IV) whether or not they had a prior cancer (p=0.375 and 0.712 for interaction between stage and OS and DSS respectively). Multivariate analysis demonstrated that whereas for both DSS and OS age, stage and non-colorectal cancer histology were independently associated with survival, a history of a previous cancer was not **(Table 2)**.

Discussion

Stringent eligibility criteria in clinical trials may be justified to ensure patient safety and the scientific value of the protocol. However, this objective may impair generalizability of trial results as many patients are excluded due to common comorbidities; most frequently for kidney, infectious, cardiac, liver or haematological-oncological disease which may not impact on the research hypothesis in question.[5] In our study we provide evidence that for patients with common gastrointestinal malignancies a prior history of a treated cancer does not result in inferior survival when compared with those patients without a previous malignancy.

Factors other than a history of a previous malignancy may influence the survival of cancer patients, and in order to address the potential confounders of age, stage and histological subtype within our study we have performed multivariate analysis using these factors as variables. Unsurprisingly, age, the presence of metastatic disease and non-colorectal cancer histology were independent predictors of survival. There are clear differences in the survival of gastrointestinal cancers based on tissue of origin and stage. For example, median survival in clinical trials for patients with metastatic pancreatic cancer is less than one year and for these patients it is unlikely that a previous cancer poses a significant competing risk for death. Alternatively, for patients with less biologically aggressive metastatic cancers such as colorectal cancer a previous cancer may represent a more frequent cause of death. However regardless of cancer subtype tumour stage remains the strongest predictor of survival in our analysis and it may be possible to argue that for all patients with advanced or metastatic incurable cancer that a history of a prior malignancy is unlikely to be relevant with respect to survival.

In our study, age was also incrementally but independently associated with reduced survival. As patients in our study with a second cancer had a mean age six years older than those without a similar history, it is possible that this is the reason that the univariate Kaplan-Meier overall survival curve appears to diverge for patients with and without a

previous cancer (we acknowledge that although this difference is non-significant the analysis may be underpowered). However, despite the fact that increasing age predicts for worse survival, there is strong support for the enrolment of older patients in clinical trials in order to increase the representativeness of clinical trial populations.[13] In contrast with increasing age, that a previous cancer does not appear to adversely affect survival provides further support for our argument against exclusion of these patients.

We note that in our study, the median time from a previous cancer diagnosis was almost eight years, which raises the question of whether the lead time from previous cancer impacts on the chances of recurrence. The low absolute numbers of patients in our study with a previous cancer make it difficult to form any meaningful observations in this regard, however we appreciate the point at which a patient may be considered "cured" of a cancer is variable –indolent hormone sensitive breast cancer or lymphomas may recur after a period of decades whereas late (> five years) recurrences of more aggressive epithelial cancers are rare. This clearly adds to the complexity of any proposal for including patients with prior cancers in clinical trials, but does not necessarily render the problem unsolvable. Due to the exponentially decreased risk of recurrence for most high grade cancers after three years this would seem a very reasonable timeframe to suggest as a cancer free baseline.

In this study population the percentage of patients with a prior cancer was 7.7%, a proportion which likely reflects the gastrointestinal cancer population studied (as second malignancies may be more common in other populations). It has been previously documented that patients with breast, prostate and colon cancer are at significantly increased risk of second malignancies, and these patients represented the majority of patients in our study.[14-16] Rates of early diagnosis and cure of these cancers are high, and may continue to increment with implementation of more comprehensive screening programmes and increasing efficacy of treatment for early stage disease.[17-19] In the

United States, the number of cancer survivors is increasing by 2% per annum and according to SEER data as many as 18% of US cancers may be a second or subsequent malignancy.[20] A recent study supports our argument – Gerber et al demonstrated that up to 80% of US ECOG sponsored or endorsed lung cancer trials excluded patients with a prior malignancy and that his affected up to 18% of lung cancer patients.[21] The same group have also recently demonstrated that both lung cancer specific survival and overall survival for lung cancer patients with a history of a prior cancer was not inferior to those without, thus supporting our hypothesis in another cancer group.[22] Our study demonstrated that 2% of the total population were potentially denied participation in a clinical trial as a result of a previous cancer. Although this is a small proportion of the total compared to the previously mentioned study it may be reflective of the patient make up of our dataset who were predominantly patients with colorectal cancer which has a weaker link to environmental exposures such as tobacco. For example, 10% of patients in our study with gastroesophageal cancer had a history of a previous cancer, possibly reflecting a stronger link in this group to underlying alcohol and smoking aetiologies. However, even if the figure of 2% is prevented from trial participation, we believe that this is unwarranted and unjust in principle. This is a significant proportion of patients to exclude from any clinical trial especially given the lack of rationale for this evidenced in our study, and in particular from randomised trials where any effect (if one existed) would be nullified by randomisation. Furthermore, when considering cancer survivors as a group, 30% of these patients were prevented from participating in trials as a result of their previous cancer. **Furthermore, when a trial was available and this group was eligible, more than half of patients chose to participate.** As advocacy groups for cancer survivors become increasingly involved in peer review of research strategies and funding, this inequity must surely be questioned.[23]

Limitations of our study include its retrospective nature and the inclusion of patients with differing cancer histologies. However, this is reflective of the patients treated at our

cancer centre, and we believe that it is generalisable to a wider population. We note that the survival of patient who did and did not participate in trials during this period was not different, which supports the external validity of these results. We chose one specific year (2006) in order to ascertain sufficient follow up of patients to detect potential recurrences and also to provide a finite timescale in which to examine the trials which were on offer at that time. **We acknowledge that our analysis could be underpowered despite containing almost 700 patients as the proportion of patients with a prior cancer diagnosis is low** and thus one might interpret any non-significant p values with caution. However in performing multivariate analysis we have attempted to demonstrate as robustly as possible within the dataset available that expected confounders of age, stage, histological subtype are independently associated with survival and that a history of a previous cancer is not. Although expanding the time scale would provide us with greater power to examine each individual histology, doing this retrospectively would prove difficult due to a lack of previous electronic records, and prospective observational studies would require significant follow up and may not provide additional information. Our study was conducted at a comprehensive cancer centre and this is evident in the high proportion of patients for whom a clinical trial was available (70%) and who participated in a trial (16% of total). Although this could potentially introduce a bias in survival times, this should apply equally to all patients as this is a single centre study. The number of patients with a previous cancer is consistent with the literature, and does not appear to have been influenced by the nature of the institution, however this may not be true of all cancers.[24]

In the UK, participation in clinical research is amongst the highest in developed countries, however the aspiration is for all patients to be offered the opportunity to participate in clinical research should they so wish, and are eligible. Governments worldwide include reducing barriers to participation in trials as a stated goal. [25] [26] However, in order to improve on current recruitment rates to cancer clinical trials it may be necessary to

question the validity of commonly held beliefs regarding eligibility. Just as older patients should not be excluded by virtue of their age alone, we argue that neither should patients with a history of an adequately treated previous cancer.[27, 28] As significant health and socio-economic inequalities have previously been identified for cancer survivors to remedy this one by providing equal access to clinical trials seems both sensible and fair.[29-31]

Disclosure of Potential Conflicts of Interest

The authors declare no conflicts of interest.

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All authors approved have the final version of the manuscript.

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Table 1: Baseline characteristics					
	No Prior Cancer		Prior Cancer		P-value
	N	%	N	%	
Gender					
Male	383	59.6	26	48.1	0.102
Female	260	40.4	28	51.9	
Age (mean)	61		67		<0.001
Diagnosis of Primary					
CRC	471	73.3	42	77.8	0.661
EGC	60	9.3	6	11.1	
HCC	27	4.2	1	1.9	
Pancreatic	85	13.2	5	9.3	
Stage of Primary					
I	19	3.0	3	5.6	0.447
II	110	17.1	12	22.2	
III	268	41.7	18	33.3	
IV	246	38.3	21	38.9	
Prior Malignancy					
Yes	0	0	54	100	
Site of Prior Malignancy					
Breast			14	25.9	
Colon			5	9.3	
Cervix			3	5.6	
Bladder			2	3.7	
Melanoma			3	5.6	
Prostate			9	16.7	
Lymphoma			2	3.7	
Ovarian			2	3.7	
Other			14	25.9	
Stage of Prior Malignancy					
I			23	42.6	
II			20	37.0	
III			10	18.5	
IV			1	1.9	

Abbreviations: CRC, colorectal cancer; EGC, esophagogastric cancer; HCC, hepatocellular carcinoma

Table 2: Gastrointestinal Cancer Survival Multivariate Analysis			
	Hazard Ratio	**95 % CI**	**p-value**
Prior Cancer	1.01	0.72 – 1.40	
Age	1.02	1.01 – 1.03	<0.001
Non CRC type	2.46	2.02 – 2.99	<0.001
Stage IV	2.98	2.48 – 3.59	<0.001

Table 3: Overall Survival Multivariate Analysis			
	Hazard Ratio	**95 % CI**	**p-value**
Prior Cancer	1.07	0.78 – 1.46	0.676
Age	1.02	1.01 – 1.03	<0.001
Non CRC type	2.40	1.98 – 2.92	<0.001
Stage IV	2.74	2.30 – 3.28	<0.001