Death from malignant disease after surgery for duodenal ulcer

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Abstract

A total of 2241 patients who had an operation for duodenal ulcer between 1947 and 1968 were followed up to determine the cause of death and to compare the observed number of deaths with the expected. Death certificates were traced for 1251 of 1387 known to have died. Observed deaths from all causes were significantly greater than expected (O/E 1.13) (95% CI 1.08 to 1.20). This was because of significant increases in deaths from neoplasms (O/E 1.25) (95% CI 1.13 to 1.39) and digestive diseases (O/E 1.71) (95% CI 1.11 to 2.59). Analysis of deaths from malignant disease showed an excess of deaths from carcinoma of lung (O/E 1.37) (95% CI 1.14 to 1.62) and from smoking related cancers (O/E 1.32) (95% CI 1.13 to 1.52) but there was no significant excess mortality from any other neoplasm. An excess of deaths within one year of the operation was seen from circulatory disease (O/E 1.85) (95% CI 1.17 to 2.78), respiratory disease (O/E 3.56) (95% CI 1.78 to 6.37), and digestive disease (O/E 21.46) (95% CI 13.75 to 31.93). These deaths are concentrated in the first postoperative month and as there is no excess mortality from circulatory, respiratory or digestive disease between 1 and 20 years postoperatively, show the direct effects of the operation as a cause of death. This together with the excess mortality from all respiratory disease confirms that excess mortality after duodenal ulcer surgery is, in the short term, the result of the operation itself and in the long term largely attributable to cigarette smoking. Operations for gastric ulcer largely account for the subsequent excess mortality from gastric cancer reported after peptic ulcer surgery. The findings do not support the theory that the operation has carcinogenic effects and do not support the case for routine endoscopic screening after operations for duodenal ulcer.

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An increase in malignant disease on longterm follow up has been reported after peptic ulcer surgery, but several studies have not supported this conclusion. The first two cohort studies by Helsingen¹ and Krause² both reported an increased risk of death from gastric cancer after surgery for peptic ulcer yet eight subsequent studies failed to confirm this.³⁻¹⁰ Six more recent studies have suggested an increased risk of death.¹¹⁻¹⁶

Increases in comparative risk for carcinoma of the bronchus,^{5,17} bladder,^{18,19} pancreas,⁵ and colon⁵ have been reported. Caygill¹⁹ also reported increases in the comparative risk of death from cancer of colon and rectum, biliary tract, female

breast, and oesophagus, yet none of these were confirmed by Moller.¹⁸

Conflicting results may have arisen because of small numbers studied, excess loss to follow up, inadequate length of follow up or failure to stratify by time. In this study we examined death in a large cohort of patients followed up for 20 to 40 years postoperatively, stratified by time, and with low loss to follow up.

Methods

All patients having an operation for duodenal ulcer at the Western General Hospital, Edinburgh between 1 August 1947 and 31 July 1968 were included in the study with the exception of those having only simple closure of perforated ulcer or under running of bleeding ulcer. Information from the case notes was recorded at the time of operation onto standard proforma. Patients were regularly followed up at a follow up clinic²⁰ or by postal review.²¹ Information about date and cause of death as reported on the death certificate was obtained from the hospital or general practitioner, supplemented by searches in the NHS Central Registers of Scotland and of England and Wales. Patients were followed up to 31 December 1988 or to death, emigration or loss to follow up if before this date. Details of underlying cause of death were taken from all death certificates that could be traced.

Each certificate was given ICD coding according to the coding instructions set out in the revision of the ICD coding in force at the time of the patients death. Significance values and confidence intervals for the comparative risks were calculated, based on an assumed Poisson distribution. As is usual, deaths above age 84 were not included in the analysis because of the probable differences between the study group and the general population in this open ended age group.

Observed numbers of deaths from major causes, including the more frequent malignant neoplasms, were compared with those expected. The latter were calculated by multiplying the person years at risk for age group, sex, and calendar period²² by the corresponding death rates for Scotland.

Results

Of 2241 patients followed up, 1387 were recorded as having died and 222 as lost to follow up before the end of 1988. Of 1387 deaths, 94 were over age 84 at death and were excluded from the analysis and of the remaining 1293, death certificates were traced for 1251, leaving 42 with unknown cause of death. These could be included only in the 'all causes' analysis. Most of

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TABLE I Observed and expected numbers of deaths (men and women) by major causes among duodenal ulcer patients

Major cause	Observed	Expected	O/E ratio	(95% CI)
Neoplasms	336	268.03	1.25*	1.13 to 1.39
Circulatory disease	445	460.36	0.97	0.87 to 1.07
Respiratory disease	134	122.72	1.09	0.79 to 1.26
Digestive disease	56	32.76	1.71*	1.11 to 2.59
All causes	1293	1139.21	1.13*	1.08 to 1.20

*p<0.001.

these deaths occurred abroad. Of 1293 patients, 993 were male (76.8%) and 300 female (23.2%). The median age at operation was 53 years (range 20–83). Fourteen (1.1%) had a Billroth I gastrectomy, 774 (59.9%) a Billroth II, 101 (7.8%) a gastroenterostomy alone, 105 (8.1%) a truncal vagotomy and pyloroplasty, and 272 (21%) a truncal vagotomy and gastroenterostomy. Table I shows that there was a significant increase in death from all causes (an observed to expected ratio of 1.13 (p<0.001) based on 1293 deaths). This mainly reflects an excess of deaths from neoplasms (O/E 1.25 (p<0.001) based on 336 deaths) and, to a lesser extent, from digestive diseases (1.71 (p<0.001) based on 56 deaths). The excess of deaths from neoplasms is mainly because of an increased mortality from lung cancer (O/E 1.37 (p<0.001) and other smoking related cancers (Table II). Deaths from smoking related cancers (lung, oesophagus, pancreas, rectum, and bladder) when considered together were increased over expected (O/E 1.32 p<0.001). Deaths from cirrhosis of the liver were also increased (O/E 2.16 p<0.05).

Death in the first postoperative year was increased (O/E 3.09 p<0.001). This is because of

an increase in deaths from digestive disease (O/E 21.46 p<0.001), respiratory disease (O/E 3.56 p<0.001), and circulatory disease (O/E 1.85 p<0.001) (Table III). These deaths were concentrated in the first postoperative month, particularly in the early part of the study, before 1960 (Table IV).

No significant excess in death from any cause was seen between 1 and 20 years postoperatively. More than 20 years after the operation death from all causes was increased (O/E 1.20 p<0.001) mainly because of the increased death from smoking related cancer and respiratory disease (Table III).

Discussion

Although the incidence and prevalence of duodenal ulcer is declining throughout the world²³⁻²⁵ it remains a common disease. Ivy²⁶ estimated that some 10% of the population of the United States would develop peptic ulcer disease in their lifetime. More recently Johnsen²⁷ found an incidence of endoscopically diagnosed peptic ulcer disease of 3.8% in normal control subjects aged between 20 and 69 in northern Norway. Until the advent of the H₂ receptor antagonists in 1975 surgical operation remained the mainstay of treatment. In Scotland in 1971, 3087 operations for duodenal ulcer were performed (Information Services Division, Scottish Health Service).

There thus remain a large cohort of patients who had duodenal ulcer surgery in the pre H₂ receptor antagonist era – that is, more than 15 years ago. Previous studies have reached differing conclusions about longterm death after surgery for peptic ulcer disease (Table V). This may have been because the studies lacked power either because they were too small, loss to follow up was excessive, the period of follow up was inadequate or there was failure to stratify by time. In this large study with minimal loss to follow up we have followed up a large cohort of patients for a minimum of 20 years and maximum of 40 after duodenal ulcer surgery, and have stratified the results by time.

There is general agreement in previously published series that after peptic ulcer surgery expectation of life is decreased compared with the general population. Ross *et al*⁵ studied 779 men from this clinic and suggested that the main causes of death in these patients were smoking associated diseases.

This study with women included, greater numbers, and longer follow up has again shown a

TABLE II Observed and expected numbers of deaths from neoplasms by site among duodenal ulcer patients (both sexes)

Site or type	ICD 9	Observed	Expected	O/E ratio	95% CI
Oesophagus	150	13	8.79	1.48	0.787 to 2.529
Lung	162	134	98.01	1.37‡	1.145 to 1.619
Stomach	151	30	28.00	1.07	0.723 to 1.529
Colon+rectum	153/154	41	32.79	1.25	0.897 to 1.696
Bladder	188	11	9.52	1.16	0.577 to 2.067
Testis	186	2	0.35	5.79*	0.694 to 2.064
Pancreas	157	14	11.47	1.22	0.667 to 2.048
Ovary	183	4	2.79	1.43	0.391 to 3.671
Prostate	185	17	12.47	1.36	0.794 to 2.183
Female breast	174	8	8.72	0.92	0.396 to 1.808
Uterus	180-2	5	3.18	1.57	0.510 to 3.669
Lymphomas	200-2	5	5.49	0.91	0.296 to 2.125
Leukaemia	204-8	5	4.96	1.01	0.327 to 2.352
Smoking related cancers†		184	139.45	1.32‡	1.136 to 1.524
All neoplasms	140-239	336	268.03	1.25‡	1.126 to 1.395

*p<0.05; †lung, oesophagus, pancreas, rectum, and bladder cancers; ‡p<0.001.

TABLE III Observed to expected ratios and observed numbers of deaths by cause and interval from operation

Site	<1 Year		Observed	1-20 Years		Observed	>20 Years		Observed	>1 Year		Observed
	O/E ratio	95% CI		O/E ratio	95% CI		O/E ratio	95% CI		O/E ratio	95% CI	
All causes‡	3.09***	2.52 to 3.75	101	1.02	0.95 to 1.09	791	1.20***	1.09 to 1.32	401	1.08**	1.02 to 1.14	1192
Neoplasms	1.51	0.75 to 2.70	11	1.19	1.04 to 1.36	215	1.37	1.13 to 1.65	110	1.25***	1.12 to 1.39	325
Stomach cancer	2.86	0.59 to 3.59	3	0.94	0.57 to 1.47	19	1.19	0.51 to 2.35	8	1.00	0.66 to 1.46	27
Colon cancer	4.62*	0.95 to 5.80	3	1.39	0.85 to 2.15	20	0.99	0.36 to 2.16	6	1.27	0.83 to 1.86	26
Smoking related cancers	0.91	0.19 to 1.14	3	1.25*	1.03 to 1.50	116	1.50**	1.16 to 1.91	65	1.33***	1.14 to 1.54	181
Circulatory disease	1.85**	1.17 to 2.78	23	0.90	0.80 to 1.01	281	1.04	0.88 to 1.23	141	0.94	0.85 to 1.03	422
Respiratory disease	3.56***	1.78 to 6.37	11	0.78	0.60 to 1.00	63	1.53***	1.17 to 1.97	60	1.03	0.86 to 1.23	123
Digestive disease	21.46***	13.75 to 31.93	24	0.98	0.60 to 1.45	22	1.08	0.52 to 1.99	10	1.01	0.69 to 1.43	32
Cirrhosis of liver	0.00		0	2.16*	0.99 to 4.10	9	1.14	0.14 to 4.12	2	1.86*	0.93 to 3.33	11

*p<0.05; **p<0.01; ***p<0.001; †these include subjects recorded as dead but without a traced death certificate; ‡smoking related cancers are oesophagus, lung, rectum, bladder, and pancreas.

TABLE IV Deaths within one year of operation

Months from operation	Year of operation			All
	1947-1949	1950-1959	1960-1968	
<1	5	39	13	57
1-2	1	11	7	19
3-6	1	8	3	12
7-12	2	6	5	13
	9	64	28	101
No of operations	149	1075	1024	

significant increase in the risk of smoking related cancers (lung, oesophagus, pancreas, rectum, and bladder) when these are considered together 20 years and more postoperatively. After this lag period there is also a significant increase in deaths from respiratory disease (Table III).

The proportion of smokers among our study group was higher than in the Scottish and UK populations during the time of entry to the study (Table VI). Some 82.9% of men smoked compared with 61% in the UK population in 1951, 54% in the UK population in 1968, and compared with 54% in the Scottish population in 1972. The proportion of women in our cohort who smoked was also higher than in the Scottish or UK population. A further example of the effect of the lifestyle adopted by this group of patients contributing to their excess mortality is again shown by the excess mortality from cirrhosis of the liver.

This study has shown the contribution of perioperative mortality to overall mortality. Deaths from all causes are significantly increased in the first postoperative year (Table III). The excess deaths from circulatory disease, respiratory disease, and digestive disease are all significantly higher. Analysis of deaths within the first year of operation (Table IV) show that the excess of first year deaths is explained by deaths in the first month. The proportion of these postoperative deaths is less in the later period of the study as would be expected because of improvements in operative and postoperative management. The increase in deaths in the first year from digestive diseases is presumably the result of misdiagnosis, a diagnosis of peptic ulcer disease having been made in patients suffering from other digestive diseases in the era before fibre-optic endoscopy was generally available.

TABLE V Risk of gastric cancer after previous peptic ulcer surgery in published works

First author	Total	Length of follow up	Cancer observed	Cancer expected	O/E ratio	95% CI
Helsingen ¹	222	10-34	11	5.2	2.12	1.06 to 3.79
Krause ²	361	23-50	25	11.3	2.21	1.43 to 3.27
Liavaag ³	616	15-35	9	9.6	0.94	0.43 to 1.78
Domellof ⁴	534	11-25	14	8.2	1.71	0.93 to 2.86
Ross ⁵	779	15-32	8	10.4	0.77	0.33 to 1.52
Clark ⁶	225	22-27	1	0.25	4.40	0 to 17.0
Shafer ⁷	338	15-40	2	2.6	0.77	0.09 to 2.78
Eriksson ⁸	1403	19-49	24	20.7	1.16	0.81 to 1.38
Tokudome ⁹	3827	10-33	34	100.6	0.34	0.23 to 0.47
Fisher ¹⁰	945	19-29	13	10.6	1.23	0.65 to 2.10
Pickford ³⁷	307	30-40	9	2.6	3.10	0.82 to 11.0
Watt ¹⁷	735	15-25	16	4.8	3.30	1.8 to 6.3
Caygill ¹¹	4466	20-40	80	50.7	1.58	1.25 to 1.96
Viste ¹²	3470	25-45	87	41.4	2.10	1.68 to 2.59
Ovaska ³²	537	10-32	12	7.7	1.56	0.62 to 3.64
Lundegardh ¹³	6459	20-33	62	37.3	1.66	1.27 to 2.13
Arnthorsson ¹⁶	1795	15-48	30	13.8	2.17	1.46 to 3.10
Offerhaus ¹⁴	2633	15-59	21	13.5	1.62	0.81 to 3.22
Toftgaard ¹⁵	2975	15-27	15	10.7	1.40	0.91 to 1.98
This study	2241	20-40	30	28	1.07	0.72 to 1.53

TABLE VI Smoking habits of patients having operations for duodenal ulcer Western General Hospital 1948-68 compared with population

	% Smokers	
	Men	Women
All operations (1948-68)	82.9	53
UK population (1951)	61	40*
UK population (1968)	54	43
Scottish population (1972)	54	43

*Data for women first became available in 1955.

This study has shown no excess of gastric cancer in patients having a previous operation for duodenal ulcer even when the lag period is 20-40 years. We believe that the conclusion of Logan and Langman²⁸ (that the evidence does not support endoscopic screening for gastric cancer in patients with previous peptic ulcer surgery) remains valid in the face of the many studies published since they reached that conclusion. This view has since been endorsed by Ovaska²⁹ and Offerhaus.³⁰ Even those studies that have claimed to show the greatest association between gastric cancer death and previous duodenal ulcer surgery have shown a much smaller excess of gastric cancer deaths compared with smoking related deaths. Thus Caygill *et al*¹¹ in a study of 2577 patients more than 20 years after duodenal ulcer surgery showed an excess of only 15 cases and no excess before then. In our study of similar size the observed number of smoking related cancers exceeded the expected by 44. Although cigarette smoking has not previously been regarded as a risk factor for stomach cancer, the British doctors study³¹ is now producing evidence to suggest that primary gastric cancer may be smoking related with a 30% excess of gastric cancer in smokers. Thus it may well be that smoking accounts for some of the excess of gastric cancer in the operated stomach.

The results of this study are broadly in line with earlier results from this clinic.⁵ With larger numbers, inclusion of women, and a longer follow up period the suggestion of a significant increase in carcinoma of the colon and rectum and of carcinoma of the pancreas have not been sustained, but, as in the previous study, there is a significant excess of observed over expected deaths when all smoking related cancers are considered together.

Our results are similar to the large Danish series of Moller and Toftgaard¹⁸ who found in duodenal ulcer patients more than 20 years postoperatively an increase in gastric cancer, which failed to reach significance and an increase in smoking related cancers. Neither our study or that of Moller and Toftgaard¹⁸ has confirmed the suggestion by Caygill *et al*¹⁹ of an increased risk of cancers of the colon, rectum, biliary tract, and female breast.

Like Moller and Toftgaard¹⁸ we can find no evidence to support the theory proposed by Caygill *et al*¹⁹ that gastrectomy produces a circulating carcinogen acting at distant sites.

A reduced or absent risk of gastric stump cancer more than 20 years after surgery for duodenal ulcer has been found in all studies apart from those of Caygill,¹¹ Viste,¹² and Ovaska.³² Tersmette *et al*³³ reviewed all the English and German language published works on this topic,

excluding those with inadequate data, insufficient numbers or sample heterogeneity. In a meta analysis of the remaining studies they found no increase in comparative risk of gastric cancer after surgery for duodenal ulcer, the increased risk of gastric cancer being seen exclusively in patients after surgery for gastric ulcer.

Many of the published studies do not discriminate between initial diagnosis of gastric and duodenal ulcer when calculating the subsequent risk of gastric cancer. It seems probable that much of the confusion in the published works results from differing proportions of gastric and duodenal ulcer patients in these series. These proportions may vary even within one country. Thus when entry began to this study the ratio of duodenal to gastric ulcer was 11.6:1 whereas in London it was 1.2:1 and this difference is probably reflected in surgical series.

It is possible that other confounding factors may explain differences in the incidence of gastric stump cancer between series. For example, gastric stump cancer incidence may be significantly related to socioeconomic group in the same way as primary gastric cancer.

It is tempting to postulate that the reported increase in gastric cancer after surgery for gastric ulcer is associated with several factors: *Helicobacter pylori* infection at an early age, which is increasingly emerging as a risk factor in gastric cancer.^{34,35} Closely associated with gastric ulcer, this in turn leads to chronic atrophic gastritis which, according to the model proposed by Correa³⁶ progresses to gastric cancer with cigarette smoking and bile salts as important cofactors. As a group patients with gastric ulcer tend to have preoperative hypo or achlorhydria, thought to be another cofactor in the development of gastric cancer, which is absent or reversed preoperatively in duodenal ulcer patients.

We conclude that there is no evidence to support the theory that operations for duodenal ulcer produce a circulating carcinogen acting at distant sites and reaffirm the view that the endoscopic screening of patients after surgery for duodenal ulcer is not justified. The greatest risks to this cohort of patients were those of the operation itself and the effects of cigarette smoking.

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