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Original Paper

Clinical Features, Frequency and Prognosis of Dukes' A Colorectal Carcinoma: A Population-based Investigation

C. Di Gregorio,[1] R. Fante,[1] L. Roncucci,[2] M.G. Tamassia,[2] L. Losi,[1] P. Benatti,[2] M. Pedroni,[2] A. Percesepe,[2] S. De Pietri[2] and M. Ponz de Leon[2]

[1]The Colorectal Cancer Study Group of the University of Modena, Dipartimento di Scienze Morfologiche e Medico Legali, 41100 Modena; and [2]Dipartimento di Medicina Interna, Università di Modena, 41100 Modena, Italy

The main aim of this study was, through the data of a population-based Registry, to establish the incidence of Dukes' A lesions by year of registration and the main clinical features, and to assess cancer-specific survival. One hundred and eighteen Dukes' A colorectal tumours were diagnosed (in 117 patients) out of 1337 registered between 1984 and 1992 in the Health Care District of Modena, Northern Italy; 94 patients were treated with surgery and 23 with endoscopic polypectomy. The frequency of Dukes' A tumours ranged between 4.8% and 18% by year of registration. Dukes' A carcinomas were significantly more frequent in the distal colon. Only 5 patients (4%) died of their cancer, and in all patients the tumour was localised in the rectum. Carcinomas associated with a poor prognosis did not show any of the biological variables usually associated with an unfavourable outcome, but, our data suggest the possibility of incomplete removal of tumours at surgery. Copyright © 1996 Elsevier Science Ltd

Key words: colorectal carcinoma, population-based, Dukes' stage

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INTRODUCTION

DUKES' A (or TNM I) colorectal carcinomas are limited to the muscular layer of the bowel wall, without invasion of adjacent tissues or distant metastasis [1, 2], and overall prognosis is usually good, with most clinical studies indicating a 5-year survival rate in the order of 80–90% [3–7]. Indeed, staging at diagnosis has been recognised as the most powerful indicator of the clinical outcome in patients with colorectal malignancies [8, 9]. However, not all investigations have shown such optimistic findings in Dukes' A carcinoma, and 5-year survival as low as 67% with a relapse rate of 41% has been reported [10]. Although the precise reasons of these less favourable results remain unclear, one of the most likely explanations is that they reflect a particular selection of the investigated cases. Most studies on Dukes' A tumours are derived from surgical series, whereas there is little information from population-based cancer registries, which do not usually report details on tumour staging [11, 12].

During the past few years, we have set up a specialised, population-based Colorectal Cancer Registry in our Health Care District [13–20]. As registration was limited to a single neoplasm, a detailed description of tumour stage at diagnosis was recorded, in addition to personal data, type of surgery and family history of cancer. From 1984 to 1992, 117 Dukes' A carcinomas from a total of 1298 registered patients were identified; this gave us a unique opportunity to analyse the main epidemiological and clinical features of a large, population-based series of relatively 'benign' colorectal neoplasms. Specific objectives of the study were (a) to establish the frequency of Dukes' A colorectal cancer—either requiring surgery or being treated with endoscopic polypectomy—by year of registration, (b) to describe the anatomical sublocalisation of these lesions in the large intestine; (c) to assess cancer-specific prognosis of these patients, making every effort in the attempt to identify all possible reasons for the clinical outcome in each patient; and (d) to

Correspondence to M. Ponz de Leon at Dipartimento di Medicina Interna, Policlinico, via del Pozzo 71, 41100 Modena, Italy.
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evaluate whether, in patients with genetically determined neoplasms, Dukes' A tumours were more frequent than more advanced lesions.

PATIENTS AND METHODS

The registry

The general organisation and the main purposes of the Colorectal Cancer Registry have been described in detail in several other reports [13–20]. In brief, the Health Care District 16 of Region Emilia-Romagna includes Modena and 10 smaller Communities comprising a total of 265 227 residents (male: 128,288; female: 136,939; census 1991). It is an entirely flat, highly industrialised area (tiles, textiles and motor cars, in particular), with one of the highest incomes per person in Italy. The population density is 450 km^2. It has been established that patients were, as a rule, registered 1–2 years after hospitalisation through consulting clinical charts, endoscopy centre records and Institute of Pathology archives. For the specific purposes of the Registry, cases identified with Death Certificates Only (DCO) have not been included in the registration.

Tumour staging

Tumours were staged using the TNM classification, which closely corresponds—as suggested by Hutter and Sobin—to the Dukes' staging into four main categories [1]. Dukes' A (or TNM I) colorectal carcinomas were limited to, i.e. did not extend beyond, the muscular wall, without infiltration of local structures, lymph nodes or distant metastasis. Histopathological diagnoses such as 'severe dysplasia', '*in situ* carcinoma' or 'neoplastic foci' were not considered to be cancer (and consequently, were not registered) unless there was a clear extension of the tumour through the muscularis mucosa [18, 19].

A total of 1337 carcinomas were registered in 1298 patients (the annual incidence rate ranging between 50 and 65 new cases/100 000 residents/year, during the study period 1984–1992). Among these, there were 118 Dukes' A lesions in 117 patients (male: 66; female: 51, mean age 67.0 ± 10.2). 29 patients had polypoid lesions which were considered suitable for endoscopic resections. In 6 of these, margins were not free of cancer and consequently, patients also underwent surgical resection. Thus, a total of 94 patients were treated with surgery (segmental resection or hemicolectomy in 89, transanal resection in 5) and 23 with colonoscopy only. Among operated patients, 66 (70%) had lesions which infiltrated the muscular wall (T2 lesions) and 28 (30%) had neoplasms limited to the submucosa (T1 lesions). Apart from staging and type of operation, the precise location in the large bowel, tumour dimensions (maximum diameter) and length of the resected tract were carefully recorded for each patient.

Assessment of survival

Assessment of the clinical outcome was one of the main objectives of the Colorectal Cancer Registry. All registered patients are prospectively followed-up working in close collaboration with pathologists, oncologists, surgeons and endoscopists. The current policy is to recommend control colonoscopy—together with CEA determination and, in selected cases, computed tomography—at regular intervals of time for at least 3 years after surgery (or endoscopic removal of cancer), with the obvious exception of patients with advanced lesions (Dukes' O) at diagnosis. Moreover, according to the latest guidelines [21–23], the majority of patients with Dukes' C carcinoma have, in recent years, been receiving combined chemotherapy. Patients who were unable to return for subsequent control were contacted by telephone, so that their status, together with the reasons for poor compliance, could be ascertained. Local recurrences, distant metastasis or metachronous tumours were verified by clinical charts, pathological reports and death certificates.

A 5-year survival rate could be estimated for all patients registered in the 3-year period 1984–1986, and the subsequent years are currently being evaluated. However, all patients with Dukes' A carcinomas in the whole series 1984–1992 were contacted, so their status could be assessed; for most of them, therefore, a complete 5-year follow-up could be traced. This, however, was limited to 4 and 3 years, for patients registered in 1991 and 1992, respectively.

Identification of HNPCC and suspected HNPCC families

In order to identify individuals and families with genetically determined tumours, we developed a stepwise procedure previously described in detail [17–19]. Briefly, individual pedigrees of patients registered between 1984 and 1992 were classified and stratified according to the presence of six clinical criteria (i.e. vertical transmission, tumour aggregation in sibships, localisation of tumours in the right colon, early age of onset, multiple primaries and mucinous histological type) all indicative of an increased susceptibility to hereditary colorectal cancer. When two or more criteria were identified, nuclear pedigrees were extended to second and third degree relatives. Extended pedigrees were then classified as HNPCC, when they met the criteria of the International Collaborative Group on HNPCC (the so-called 'Amsterdam criteria') [18] or 'suspected HNPCC' when: (a) at least two successive generations were affected by colorectal cancer (or tumour of the HNPCC spectrum); (b) at least one case was diagnosed under the age of 55 years; and (c) in the sibship of the proband, 50% or more of the siblings were affected by cancer [19].

Biological, morphological and clinical variables; statistical analysis

One of the main objectives of the present study was to identify possible reasons for the poor clinical outcome observed in a few Dukes' A patients (see Results). Tumours in subjects who died of their neoplasms were therefore analysed for a series of variables which might have prognostic relevance [24, 25]. Grade-related parameters (i.e. degree of differentiation, extent of fibrosis, pattern of growth, lymphocytic infiltration, mucinous histological type) were carefully evaluated as already reported [23, 25]. Moreover, nuclear ploidy (by flow cytometry) and the expression (by immunohistochemistry, with the Pab 1801 antibody) of the *TP53* tumour suppressor gene were also evaluated as previously described in more detail [26]. These data were compared with two control series: (a) Dukes' A carcinomas with a favourable outcome ($n = 49$); and (b) all Dukes' B tumours ($n = 94$) registered in the 3-year period 1984–1986. Differences in the occurrence of total and Dukes' A carci-

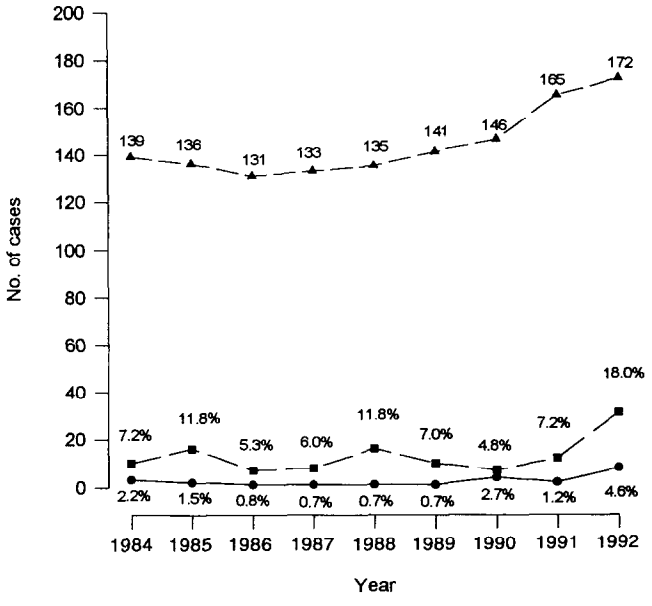

Figure 1. Frequency of Dukes' A carcinomas by year of registration (1984–1992, Colorectal Cancer Registry of the Health Care District of Modena, Northern Italy). Total number of registered patients (all stages, - -▲- -); Dukes' A tumours (- -■- -); and malignant polyps resected during endoscopy (—●—).

nomas in the various tracts of the large bowel were assessed with the chi-square test.

RESULTS

The frequency of Dukes' A carcinomas, by year of registration, is illustrated in Figure 1. Dukes' A tumours ranged from a minimum of 4.8% of all registered neoplasms in 1990 to a maximum of 18% in 1992 (average 8.8%, confidence intervals 6.1–11.5). Polyps (more specifically lesions treated by endoscopy only) represented a small fraction of all Dukes' A cases in each year of registration.

Table 1 compares the distribution of all registered colorectal carcinomas (of various stages) with that of Dukes' A lesions. As expected, most of these tumours were localised in the distal large bowel (rectum, recto-sigmoid junction and sigmoid). However, Dukes' A carcinomas did not represent a constant fraction of cases in each sublocalisation, but showed a significantly ($\chi^2 = 6.2$; $P < 0.01$) relative excess in the distal left colon, where their proportion was in the order of 10–12% of all cases, against 2–5% in the other intestinal segments.

Table 1. Distribution of all registered colorectal carcinomas (1337) and of Dukes' A lesions (n = 118) in the various tracts of the large bowel

Site	Registered tumours (*n*)	Dukes' A tumours (*n*) (%)
Rectum	490*	62* (12.7)
Sigmoid	347	37 (10.7)
Descending	85	2 (2.4)
Transverse (with flexures)	171	6 (3.5)
Ascending	96	5 (5.2)
Caecum	125	4.8
Anus	14	6 —
Appendix	3	0 —
Not specified	6	0 —

* 84% of Dukes' A tumours were localised in the rectum or sigmoid while only 63% of tumours of all stages were similarly located ($P < 0.01$).

Table 2 summarises survival and mortality data for all patients with Dukes' A lesions. Among the 23 subjects treated endoscopically, 18 were alive at 5 years; the remaining 5 individuals died for various reasons but not for recurrent or metastatic colorectal cancer. Thus, there was no death, in this subgroup, that could be attributed to the original lesion. 77 of the 94 patients who underwent surgery were alive at 5 years (82%), 3 died within one month of surgery (and were therefore considered peri-operative deaths), 7 died from causes unrelated to colorectal cancer, and 2 for reasons which could not be specified. In only 5 patients (5%) was death attributable to the neoplasm, and these had cancer localised in the rectum and died for documented local recurrence. The clinical features of these 5 individuals are shown in more detail in Table 3; there were no marked differences as far as age, sex, dimension of tumours and of the resected tract of intestine were concerned between these patients and those who survived. However, all 5 patients with a poor prognosis had tumours in the rectum, and 3 of them (60%) were treated with abdominoperineal resection (Miles operation), a type of surgery which was much less common among survivors (6%). Similar inconsistent findings were seen when morphological or biological variables were taken into consideration (Table 4). Indeed, tumours of patients with a poor outcome were almost all diploid and well differentiated, two parameters which are usually associated with a more favourable prognosis [25, 27].

The proportion of Dukes' A tumours or more advanced lesions among HNPCC patients was not different from that of the whole series of registered patients; similar findings were observed in suspected HNPCC families (data not shown).

DISCUSSION

The proportion of Dukes' A carcinomas observed in this study (118 of 1337 registered tumours, 8.8%) is in close agreement with the figures reported by other investigators [28–30], which are appreciably less than those seen in some American series [31, 32]. While the reasons for these differences remain unclear, it is likely that they reflect—at least in part—the frequency with which sigmoidoscopy or colonoscopy are carried out in a given population. In addition, possible inclusion of dysplastic or '*in situ*' lesions (not considered as cancer in the present and in many other series) may account for the different figures. Finally, bias due to selection of patients in surgical series cannot be excluded. This possible selection bias clearly does not apply to population-based investigations, where all tumours developed in a well-defined area are considered, and incidence rates calculated with the resident population as a denominator.

A higher frequency of Dukes' A lesions in the distal large bowel has been reported by other authors and can be interpreted in physiopathological terms. Tumours of the proximal colon tend to be less symptomatic than neoplasms developed in the distal intestine, whose presence might be revealed more easily be bleeding, pain or other symptoms of obstruction. Thus, we can speculate that tumours of the

Table 2. Clinical data (survival and mortality) for all patients with Dukes' A lesions registered in Modena between 1984 and 1992 (total = 117)

	Patients treated with surgery	Patients treated with endoscopy	Total
Total registered	94	23	117
Alive at 5 years*	77 (82%)	18 (78%)	95 (81%)
Peri-operative mortality	3 (3%)	0	3 (3%)
Deceased for causes unrelated to colorectal tumours	7 (7%)†	5 (22%)‡	12 (10%)
Deceased for recurrent or metastatic colorectal cancer	5 (5%)	0	5 (4%)
Deceased for reasons remaining unclear	2 (2%)	0	2 (2%)

* For patients registered in 1991 and 1992, follow-up was limited to 4 or 3 years; †Causes of death: stroke (2), heart attack (2), myeloma, bladder cancer, gastric carcinoma; ‡Causes of death: stroke (2), heart attack, prostate cancer, lung cancer.

Table 3. Clinical features of Dukes' A patients who died of colorectal cancer and of a control group

Patient	Age (years)	Sex	Tumour site	Stage	Tumour dimension (mm)	Resected specimen (mm)	Type of surgery	Cause of death	Interval surgery–death (months)
1	64	F	Rectum	T2	40	260	Miles	L.r.	54
2	48	M	Rectum	T2	50	200	Miles	L.r.	36
3	73	F	Rectum	T2	42	55	T.r.	L.r.	24
4	71	F	Rectum	T2	30	200	Miles	L.r.	38
5	54	F	Rectum	T2	23	140	S.r.	L.r.	52
Mean	62.2 ± 9.0	F = 80%	Rectum = 100%		37.5 ± 9.5	171 ± 77	Miles = 60% S.r. = 20% T.r. = 20%	L.r. = 100%	40.8 ± 12.4
Controls*	65.4 ± 6.8	F = 54%	Rectum = 60%		40.0 ± 15.0	214 ± 129	Miles = 6% S.r. = 68% T.r. = 26%		

L.r., local recurrence; T.r., transanal resection; S.r., segmental section. *Two control series registered in the period 1984–1986 (i.e. Dukes' carcinomas with a favourable outcome and Dukes' B carcinoma).

caecum, ascending and transverse colon may grow without symptoms for a long time. This is also true for most of the rectal and sigmoid cancers, though it is likely that a higher fraction of these would become symptomatic and be diagnosed at an earlier stage. Finally, we expected to see many more tumours which could be treated with endoscopic polypectomy; indeed, only 23 of 118 Dukes' A lesions (19.5%; but 1.7% considering the whole series of 1337 registered tumours) could be managed by the endoscopist. These findings highlight, once again, the importance of the population-based approach in providing the 'true dimension' of a given clinical observation, which may only appear to be more frequent because of a particular selection of the study group [33–35]. Finally, at variance with the American series [36] showing an increased proportion of Dukes' A lesions among HNPCC patients, our findings did not show any tendency towards a more favourable staging for genetically determined colorectal tumours.

The results of this study confirm the overall good prognosis of Dukes' A colorectal carcinoma; indeed 5 patients only, out of 117, (4%) died of their cancer, whereas deaths for other reasons were more frequent, a finding which can be attributed to the advanced age of many patients. These observations are consistent with most data in the literature [5–7, 37–39] on colorectal cancer survival. The relevance of our approach stems not only from its population-based design, but also from the meticulous assessment of all causes of death. This included telephone calls to almost all patients

Table 4. Biological characterisation of the 5 patients with Dukes' A lesions who died of their disease. The data are compared to those of two previously reported [24] control series registered in the period 1984–1986 (i.e. Dukes' A carcinomas with a favourable outcome and Dukes' B carcinomas)

	Dukes' A (deceased) (n = 5)	Dukes' A (surviving) (n = 49)	Dukes' B (n = 94)
Differentiation			
Well	4	41%	20%
Moderate	1	53%	66%
Poor	0	6%	14%
Lymphocytic infiltration			
Absent or little	3	28%	16%
Moderate or extensive	2	72%	84%
Extent of fibrosis			
Absent or little	3	49%	34%
Moderate or extensive	2	51%	66%
Pattern of growth			
Expanding	4	96%	69%
Infiltrating	1	4%	31%
Amount of mucin			
<50%	4	98%	92%
>50%	1	2%	8%
Nuclear ploidy			
Diploid	5	69%	59%
Aneuploid	0	31%	41%
TP53 expression			
Positive	4	33%	40%
Negative	1	67%	60%

and/or relatives, and accurate pathological verification of morbidity and mortality.

Despite all our efforts, the reasons why 5 patients (all with T2 lesions localised in the rectum) died of recurrent colorectal cancer remain unclear. As shown in Table 4, these lesions did not seem particularly 'aggressive', in that they were not associated with some of the morphological/biological variables (aneuploidy, *TP*53 expression, infiltrating pattern of growth) which have been associated with a more severe prognosis [22, 25, 40]. Similarly, none of the clinical features (Table 3) could give any suggestion for the possible different nature of these tumours. We are led, therefore, to suspect that Dukes' A carcinomas with a recurrent or metastatic clinical course were not completely removed at surgery, and this implies understaging at diagnosis. The fact that all 5 patients had rectal tumours reinforces this possibility. Neoplasms of the distal 8 cm of large bowel require more complex surgery, owing to the limited dimensions of the pelvis and, consequently, the risk of an incomplete removal of the neoplastic tissue is increased [41].

Although the data are limited to a series of 118 consecutive early colorectal lesions, a small fraction of which treated at endoscopy, our findings seem to suggest that Dukes' A carcinomas should be viewed as 'benign' and treatable malignancy. The 100% success rate, however, is observed only with T1 lesions and with cancers removed at endoscopy (which are, by definition, T1 tumours). Our results, therefore, seem to suggest a more widespead use of lower endoscopy (especially in high-risk individuals) in the attempt to increase the proportion of tumours diagnosed at this stage and the fraction of cases treated with endoscopic polypectomy. In addition, since all 5 patients who died of Dukes' A rectal tumours had local recurrence, the present findings stress the importance of adequate mesorectal excision in patients with cancer of the rectum.

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