Changing practices for diagnosis and treatment of colorectal cancer in Calvados: 1990-1999

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SUMMARY

Aim — Two consensus conferences on management of colorectal cancer were conducted in France during the last ten years: one regarding rectal cancers in 1994 and the other regarding colonic cancer in 1998. In the present study, we examined data collected in a local gastrointestinal cancer registry to investigate changes in management practices for colorectal cancer in a well-defined population seen between 1990 and 1999.

Methods — The study population consisted of 3,135 patients with colorectal cancer diagnosed in Calvados (an administrative district in northern France) from 1990 to 1999. Two periods were defined: P1 = 1990-1994 and P2 = 1995-1999. Multivariate logistic regression analysis was performed.

Results — No trends in stage of disease at diagnosis or rate of surgical resection were observed. For patients with cancer of the rectum, the rate of sphincter preservation increased significantly from 65.6% in P1 to 72.3% in P2, in men and in all patients under the age of 75 years. For patients with cancer of the colon, the number of resection specimens with at least eight examined lymph nodes increased from 50.7% in P1 to 60.2% in P2. This trend predominated in university centers; for rectal cancer patients it was significant only in university centers. Prescription of adjuvant chemotherapy for stage III colonic cancer increased significantly: 41.4% in P1 and 52.5% in P2. No changes in prescription of adjuvant radiotherapy for rectal cancer were observed, irrespective of the stage at diagnosis. The proportion of patients managed in university centers decreased significantly over time from 30.5% in P1 to 27.6% in P2, with a corresponding increase in private clinics.

Conclusion — Most of the trends observed during the study period began before the consensus conference guidelines were issued. The consensus guidelines appear to have influenced management practices mainly in university centers, while the majority of patients are managed in non-university centers.

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Évolution des pratiques diagnostiques et thérapeutiques du cancer colorectal dans le département du Calvados entre 1990 et 1999

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Résultats — Aucune modification du stade au diagnostic ni du taux de résection chirurgicale n’a été observée entre les 2 périodes. Concernant le cancer du rectum, la conservation sphinctérienne (65,6 % en P1 et 72,3 % en P2) a significativement augmenté chez l’homme et chez les malades de moins de 75 ans. Concernant le cancer du côlon, la proportion de pièces d’excérèse avec au moins 8 ganglions examinés a augmenté : 50,7 % en P1, 60,2 % en P2. L’augmentation la plus marquée concernait les centres universitaires. Concernant le cancer du rectum, cette progression n’était significative que dans ces centres universitaires. Concernant le cancer du côlon, la chimiothérapie adjuvante a significativement augmenté pour les cancers de stade III : 41,4 % en P1, 52,5 % en P2. Concernant le cancer du rectum, la fréquence de la radiothérapie adjuvante n’a varié pour aucun stade. Globalement, la proportion de cancers pris en charge dans les centres universitaires a chuté significativement (30,5 % en P1, 27,6 % en P2) au profit des établissements privés.

Conclusions — La plupart des évolutions observées ont débuté avant les conférences de consensus. Lorsqu’ils existent, les effets des conférences de consensus semblent limités aux centres universitaires alors que la majorité des malades est prise en charge ailleurs.

In France, a wide spectrum of institutions, from university centers to private clinics, provide care for patients with colorectal cancer (CRC). Comparisons of healthcare practices between these different types of institutions is difficult because cohorts of patients reported by specialized hospital centers are not representative of the patient populations under-going routine care in other institutions. Trends in routine management practices are however accurately reflected by cancer registries which provide exhaustive data for a given geographical region.

At a consensus conference held in Paris in January 1998, a group of experts examined therapeutic advances in the field of colonic cancer and established a certain number of management guidelines [1]: (a) It was recommended that pathology reports of surgical specimens should use the pTNM system and detail the status of the surgical margins, the histological type of cancer, the degree of perirectal invasion, and the number of metastatic nodes
examined [2-4]. At least 8 nodes must be examined in order to avoid under-staging (false stage II) which would have an important impact on therapeutic decision-making and prognosis [5-7]; (b) For stage III disease, adjuvant chemotherapy has proven efficacy, improving survival by 10 to 15% compared with surgery alone [8-10]; (c) Conversely, considering currently available evidence, adjuvant chemotherapy has no proven efficacy in stage II disease and should not be prescribed outside of therapeutic trials [11, 12]; (d) For stage IV colonic cancer, palliative chemotherapy has been shown to improve quality-of-life and lengthen median survival by six months.

For cancer of the rectum, a consensus conference was held in Paris in December 1994, leading to several recommendations [13]: (a) For tumors involving the mid-third of the rectal ampulla, the sphincter should be preserved whenever possible; (b) Preoperative radiotherapy is indicated for resectable locally-advanced cancers (T3, T4, N+, N+) due to the risk of local recurrence; (c) Indications for postoperative radiotherapy are limited to exceptional cases where the tumor stage is underestimated before surgery or in the event of first-line surgery. The conference did not make any recommendations concerning the pathology report; no guidelines were established for recording the number of nodes to examine or reporting the status of the surgical margins necessary for classifying resection as R0 or R1.

The purpose of the present work was to investigate changes in diagnostic and therapeutic practices for patients with colorectal cancer treated in the French administrative district of Calvados between 1990 and 1999 and to determine the influence of the consensus guidelines on these practices.

**Patients and methods**

The social and demographic characteristics of the patients, tumor data, and diagnostic and treatment modalities were collected retrospectively using information provided by the Calvados Registry of Gastrointestinal Tumors. This Registry had 3 135 incident cases between January 1, 1990 and December 31, 1999 in Calvados. This population was composed of 1 663 men (53%) and 1 472 women (47%). Mean age was 70 years with 35.2% of the patients aged 75 years or older at the time of diagnosis. Among these 3 135 incident cases, 2 200 (70.8%) were colonic cancers, including tumors of the rectosigmoid junction, and 915 (29.2%) were tumors of the rectal ampulla. Twenty variables recorded in the Registry data were studied: residence, age, gender, month of diagnosis, tumor topography (colon or rectum), clinical signs, presence or not of synchronous organ metastasis, and type of managing institution (university hospital, regional anticancer center, general hospital, private clinic). The following variables were recorded from histology reports of surgical resected specimens: number of nodes examined, number of invaded nodes, parietal extension, invasion of proximal, distal, and lateral resection margins, histological stage (pTNM classification). Type of surgery (scheduled versus emergency) and use of adjuvant or neoadjuvant radiotherapy or chemotherapy were also noted.

**Statistical analysis**

Statistical analysis was performed with BMDP 4F, 1L and 2L modules. Comparisons were performed with chi-square test for qualitative variables and Student’s t test for quantitative variables. P < 0.05 was considered significant. Univariate analysis of changes in practices over time was performed by applying the chi-square trend test to annual rates (P < 0.05). Multivariate analysis was performed to search for changes in healthcare practices over time after adjusting for potential confounding factors using the ascending step-by-step logistic regression method with a significance threshold set at 10%. Raw and adjusted odds ratios were calculated with their 95% confidence intervals. Two periods, 1990-1994 and 1995-1999, were considered since logistic regression requires a bimodal dependent variable. For the 1998 histology reports, we compared real rates observed on surgical specimens having at least eight examined nodes with expected rates determined by linear logistic regression (least squares method) using coefficients projected from the preceding years (1990-1997).

**Results**

**Type of healthcare institution**

Care for patients with colorectal cancer was provided by a wide variety of institutions. The proportion of patients treated at university centers (University Hospital or Regional Anti-Cancer Center) declined significantly over time, with a corresponding increase in the proportion of patients treated in private clinics (figure 1). This trend was comparable for both cancer of the colon and rectum. In 1999, 28.4% of the patients with colorectal cancer were treated in university centers, 11.3% in general hospitals, and 50.6% in private clinics. We searched for factors associated with care in private clinics examining gender, age (< 75 yr versus ≥ 75 yr), cancer stage, and period (P1 = 1990-1994, P2 = 1995-1999). After adjustment for age and gender, logistic regression multivariate analysis demonstrated that tumor stage and period of care were significantly and independently correlated with the type of institution providing care: the proportion of patients receiving care in private clinics increased over time with a trend toward less advanced tumors (table I).

**Stage at diagnosis**

Stage at diagnosis did not change significantly between 1990 and 1999 for either colonic or rectal cancer. Staging for colorectal cancer. Multivariate analysis of factors associated with management in private centers.

Cancer colorectal. Analyse multivariée des facteurs associés à la prise en charge dans les établissements privés.

<table>
<thead>
<tr>
<th>Stage at diagnosis</th>
<th>Adjusted RR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stages**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.78</td>
<td>0.66-0.92</td>
</tr>
<tr>
<td>3</td>
<td>0.09</td>
<td>0.05-0.16</td>
</tr>
<tr>
<td>Periods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (1990-1994)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2 (1995-1999)</td>
<td>1.40</td>
<td>1.18-1.64</td>
</tr>
</tbody>
</table>

RR: relative risk; 95% CI: 95% confidence interval; * adjusted for age and gender; ** stage I = TNM I or II; stage 2 = TNM III or IV; stage 3 = not operated.
the overall population was: stage I, 22.2%; stage II, 25.3%; stage III, 22.7%; stage IV, 19.3%. Stage I tumors were more frequent for cancer of the rectum (28%) than for cancer of the colon (19.8%). Tumor stage was unknown for 4.1% of the patients and 6.4% of the patients did not undergo surgery. The rate of synchronous organic metastasis did not change between 1990 and 1999, with an overall rate of 20.3% for the colon and 16.9% for the rectum (figure 2).

Surgical treatment

The rate of resection was high for colonic cancer and did not change over the ten years studied. For the entire study population, surgical resection was performed in 90.9% of the patients (including 8.8% endoscopic procedures) and palliative surgery in 3.4%. Surgery was not attempted in 5.6% of the patients. When data were available, we distinguished scheduled surgery from emergency surgery, the latter of which was performed in 22.3% of the operated patients (this rate did not change significantly over time). Emergency procedures were more frequent in general hospitals than in university centers or private clinics (25.6%, 18.5% and 15.6% of surgical procedures for colonic cancer, respectively).

For rectal cancer, 82.6% of the patients underwent tumor resection (including 13.6% endoscopic procedures) and 4.5% palliative surgery. Surgery was not attempted in 12.9%. The rate of surgical resection did not vary over time. Among the surgical resections (excluding endoscopic procedures), sphincter function was preserved in 69.3%. This rate did not change significantly: 65.6% for 1990-1994 and 72.3% for 1995-1999 (P = 0.1). Procedures with preservation of sphincter function were performed more often in university centers than in general hospitals or private clinics: overall rate = 75.2%, 60.8% and 68.7% in university centers, general hospitals, and private clinics, respectively (P < 0.05). The rate of sphincter preservation increased significantly in men (P = 0.009) but not in women, and in subjects aged less than 75 years (P < 0.05) but not in those aged over 75.

Pathology reports

The number of lymph nodes examined for patients who underwent tumor resection (excluding endoscopic procedures) for pTNM stage I, II, and III cancer was not recorded in 14.6% of the pathology reports established during the ten years of the study; the rate declined from 25.5% for 1990-1994 to 3.2% for 1995-1999 (P < 0.01).

Since the consensus conference on colonic cancer recommended examining at least eight nodes to establish precise staging, we examined this criteria over the ten years. The University Hospital and the Regional Anti-Cancer Center both have their own pathology laboratory while the other healthcare institutions refer their surgical specimens to private pathology laboratories. Over the ten years of the study, 56.5% of the pathology reports mentioned eight or more examined nodes, with an increase over time from 51.8% for 1990-1994 to 60.3% for 1995-1999 (P < 0.001). This proportion was higher for patients treated in university centers (64.6%) than in general hospitals (52.3%) or private clinics (55.9%). The proportion of pathology reports mentioning examination of at least eight nodes increased significantly over time in all institutions (figure 3) and remained significant (table II) after adjustment for type of institution. For 1998, the year following the consensus conference, the number of pathology reports mentioning at least eight nodes after resection of a colonic tumor was greater than the number predicted by the least squares projection from the preceding years (76.8% observed versus 62.5% expected). For cancer of the rectum, the overall percentage of pathology reports mentioning examination of at least eight nodes was 43% (49.1% for the university centers, 39.1% for general hospitals and 41.3% for private clinics). Unlike the trend observed for colonic cancer, this overall rate did not change over time for rectal cancer with 42.3% for 1990-1994 and 43.5% for 1995-1999. There was however a significant increase in this rate for patients treated at the university centers: 34.3% in 1990-1994 and 60.4% in 1995-1999 (P < 0.001). Surgical clearance, reported as the histological status of the surgical margins allowing a classification as complete (R0) or incomplete resection (R1), was detailed on only 21.6% of the pathology reports of rectal cancer in 1999.

Table II – Colonic cancer. Multivariate analysis of factors associated with at least eight nodes examined.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted RR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>University Center**</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>General Hospital</td>
<td>0.60</td>
<td>0.42-0.86</td>
</tr>
<tr>
<td>Private Clinic</td>
<td>0.65</td>
<td>0.48-0.87</td>
</tr>
<tr>
<td>Period 1 (1990-1994)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Period 2 (1995-1999)</td>
<td>1.53</td>
<td>1.19-1.96</td>
</tr>
</tbody>
</table>

RR: relative risk; * adjusted for age and gender; 95% CI: 95% confidence interval; ** University Hospital and Regional Anti-Cancer Center.
Adjuvant treatment

CHEMOTHERAPY FOR COLONIC CANCER

These results concern patients who underwent tumor resection (excluding endoscopic procedures) with a known pTNM stage. Adjuvant chemotherapy was prescribed for 21.8% of all patients with stage II cancer, a rate which did not change over the ten years of the study. Again considering all treatment centers, adjuvant chemotherapy was prescribed for 46.9% of the patients with stage III cancer, with a significant increase over time (P < 0.0001). This trend was significant in all types of treatment centers (figure 4) but did not become more pronounced after the 1998 consensus conference. At univariate analysis, age was found to be a limiting factor for chemotherapy with, for the ten years of the study, 10.7% of the patients aged 75 and older being given chemotherapy. This rate increased over time: 6.4% for 1990-1994 and 15.3% for 1995-1999 (P = 0.03). The age effect remained significant after multivariate analysis including the age, type of center, and period variables, demonstrating an under-treatment of patients aged 75 years and older and a restriction of indications in general hospitals compared with university centers (table III). For stage IV colonic cancer, 45.9% of the patients were given palliative chemotherapy, a rate which progressed significantly over the ten years from 41.3% for 1990-1994 to 50.2% for 1995-1999 (P < 0.05). Age remained an important factor also limiting the prescription of chemotherapy (figure 5).

RADIOTHERAPY FOR CANCER OF THE RECTUM

Overall, 53.1% of the patients with stage II and III cancer of the rectum (pTNM classification) were given radiotherapy. This rate did not change over time in any of the treatment centers. Radiotherapy was prescribed preoperatively 9 out of 10 times during the study. Radiotherapy was much less frequent in patients aged 75 years or older than in younger patients (figure 6).

CHEMOTHERAPY FOR CANCER OF THE RECTUM

The overall rate of chemotherapy for stage II cancer of the rectum was 29.3% with 18.4% for 1990-1994 and 26.2% for 1995-1999 (P < 0.02). For stage III tumors, 38.4% of the patients were given chemotherapy with no significant change over time. For stage IV tumors, the rate was the same as for colonic cancers, 40.9% with no change over time.

Discussion

Population studies provide good insight into real clinical practices for a given population of patients treated in a designated geographical area, avoiding the selection biases inherent in university hospital-derived cohorts. This point is

<table>
<thead>
<tr>
<th>Table III. Multivariate analysis of factors associated with adjuvant chemotherapy in patients with TNM stage III cancer of the colon.</th>
<th>Adjusted RR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 75 years</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≥ 75 years</td>
<td>0.10</td>
<td>0.06-0.16</td>
</tr>
<tr>
<td>Type of institution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>University Center**</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>General Hospital</td>
<td>0.37</td>
<td>0.20-0.71</td>
</tr>
<tr>
<td>Private Clinic</td>
<td>0.88</td>
<td>0.53-1.47</td>
</tr>
<tr>
<td>Period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (1990-1994)</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*RR: relative risk; ** University Hospital and Regional Anti-Cancer Center.
particularly important for colorectal cancer due to the fact that many patients are treated outside university centers. In our region of northern France, more than 50% of the patients are treated in private institutions, a trend that has grown since the national study conducted in 1990 [14]. Our results describe several trends but also raise some doubts concerning the impact of the French consensus guidelines proposed for all healthcare centers.

Tumor stage at diagnosis has evolved little in Calvados. Limited cancers (stages I and II) account for 47.5% of cases, a situation less favorable than in another region of France, Côte d’Or, where 36.5% of the colorectal cancers diagnosed between 1990 and 1998 were stage I or II [15]. Beyond these trends, it is noteworthy that implementation of organized screening for colorectal cancer, as advocated by the consensus conference in 1998 and which would be the only way of increasing the rate of early-stage diagnosis, has been slow.

The rate of surgical resection, now greater than 90% for the colon and about 80% for the rectum, has been very high since the early nineties. In this older population, it is difficult to foresee any further progress in this rate in the upcoming years. In other European countries, the rate of resection has varied; the highest rates are observed in France [15], the Netherlands, and Italy. The lowest rates are observed in Spain, Poland, and the United Kingdom [16]. Several reports have noted that age has an effect on rate of resection [17, 18], but sometimes only for very elderly patients, as was observed in our population and in the Rotterdam registry where the rate of resection did not decline until the age of 89 years [19]; this contrasts with the figures from the United Kingdom where only 72% of the patients aged over 75 years underwent tumor resection [20].

In our population, 22.3% of patients with colonic cancer underwent emergency surgery. This rate is higher than reported in Côte d’Or (13.7%) for 1976-1998 [15]. Half of the patients in the Côte d’Or series had a temporary stoma, a common procedure during emergency surgery for intestinal obstruction or perforation. In a report on seven administrative regions in France, the rate of stoma for colonic cancer was 17.4% in 1990 and 16.8% in 1995 [14]. The rectal ampulla was preserved in nearly 70% of the rectal cancer patients, a rate which had been achieved in the early nineties. The 1994 consensus guidelines do not appear to have had much effect on the overall rate nor on the different surgical approaches used in university or non-university centers.

Looking at the number of nodes examined after resection of colorectal tumors, the overall trend appears to be satisfactory as seen by the constant increase in the number of pathology reports mentioning the designated number of eight nodes, particularly during the two years after the consensus conference in 1998. Nevertheless, the consensus guidelines do not appear to have had a uniform impact since the difference between university and non-university centers in the percentage of pathology reports complying with the recommendations persisted over time. During the last two years of this study, one-third of the pathology reports for patients treated in non-university centers show that less than eight nodes were examined. This is a meager progress since 1995 when a national study noted that 59.7% of the reports mentioned the designated eight nodes [21].

Use of adjuvant chemotherapy for stage III coloncancer has evolved since the proof of its efficacy was published in 1990 [8]. Adjuvant chemotherapy was used earlier in our region and for more patients than in the Côte d’Or where 13.5% of patients were given chemotherapy between 1989 and 1993 [15]. Chemotherapy is however used less often in these two regions than in the United States where 43% of patients were given chemotherapy during the same period [22]. The 50% threshold was reached or exceeded only during the very last years of the study, with persistence of differences between treatment centers; overall progress has nevertheless been achieved since 1995 where the overall rate of chemotherapy varied from 38.1% to 50% in seven administrative regions in France [14]. Age remains an important factor limiting the prescription of chemotherapy, but considering the low toxicity of the drugs used and the improved life expectancy, there is undoubtedly a risk of under-treating older patients. It would be useful to conduct therapeutic trials specifically designed for evaluating chemotherapy in older patients, as was recently proposed by the Federation of French-speaking Gastrointestinal Cancer Specialists. Inversely, although the usefulness of chemotherapy for stage II tumors remains controversial — a meta-analysis of five randomized trials [23] was unable to demonstrate any improvement in survival — one patient out of five has been given chemotherapy since the early nineties. We thus have a paradoxical situation where, on one hand, full deployment of chemotherapy is slow in coming for indications where it has scientifically proven efficacy, while on the other hand, it is widely used for a more controversial indication; this was previously demonstrated in a French national study in 1995 where the rate of chemotherapy was 10 to 35.4% in seven administrative regions [14]. The subjective nature of chemotherapy prescription is particularly striking for rectal cancer where frequent use appears to arise more from simple analogy with cancer of the colon than from evidence-based scientific rationale or consensus guidelines. Looking at adjuvant radiotherapy for rectal cancer, the 1994 consensus appears to have had little effect since the maximal rate, close to 50%, was reached early during the study period, almost always with a preoperative protocol.

In conclusion, even though certain practices have evolved in line with practices recommended by the 1994 and the 1998 consensus conferences, little progress has occurred in certain areas, particularly concerning prescription of adjuvant treatments for older patients, use of common practices in all healthcare institutions, and establishing standard quality control procedures. Despite these observations, changing practices, associated with progress in early-stage diagnosis and in reduced operative mortality, have enabled clear improvement in patient survival in Côte d’Or from 1976 to 1998 [15]. Changing practices appear to be largely independent of guidelines proposed by consensus conferences. It would therefore be useful to evaluate the real efficacy of consensus guidelines. Focus should now be placed on consensus conference organization; impact studies conducted with adapted methodologies could provide a valid assessment of guideline diffusion to concerned healthcare providers. Similarly, development of pluridisciplinary oncology concentration units operating within the different institutions would be helpful in promoting application of conference guidelines.

REFERENCES


