



X Simposio Internacional

AVANCES EN EL TRATAMIENTO
DE TUMORES DIGESTIVOS

ZARAGOZA
13/14 DE DICIEMBRE DE 2002

Ponencias

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Organizado por



Grupo Español de Tratamiento
de los Tumores Digestivos

Auspiciado por:



SOCIEDAD
ESPAÑOLA
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ASOCIACIÓN
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Celecoxib in the Prevention of Gastrointestinal Tumours

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Twenty years ago, cancer was considered an empiric clinical "event." Technologic innovations (e.g., endoscopy, imaging, mutation analysis) are providing greater access to subclinical neoplasia, therefore we now recognize that cancer is less an event, than one late step in a prolonged evolutionary process. With that understanding, come time, targets, opportunities - even responsibilities - for intervention long before the development of cancer. Molecularly-targeted preventive interventions (chemoprevention) offer an attractive, mechanistically-based approach to interrupt or retard the neoplastic process.

Cyclooxygenase (COX) -1 and -2 enzymes convert arachidonic acid into prostaglandins (PGs) and thromboxanes, thereby contributing to the carcinogenic cascade¹. Multiple solid tumors (e.g., colon, lung, prostate, breast, skin, esophagus, pancreas, bladder) over-express COX-2 and produce more PGs (particularly PGE₂) than healthy tissues from which they are derived². In the colorectum, 50% of adenomas and 80% of carcinomas over-express COX-2, making the COX-2 enzyme a particularly appealing target for chemoprevention. Predictably, the accumulated data on chemopreventive efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs, also known as non-selective COX inhibitors) are most compelling in colorectal cancer where over 25 years of epidemiologic, pre-clinical, and now clinical data confirm anti-proliferative and pro-apoptotic effects³. Despite such persuasive data, the development of NSAIDs for chemoprevention has been hampered by gastrointestinal toxicities largely attributable to COX-1 inhibition and safety concerns associated with long-term administration. The therapeutic index of NSAIDs improved with the discovery of COX-2 selective inhibitors (such as celecoxib and rofecoxib) that were recently approved for use as anti-inflammatories, and have subsequently become lead compounds for cancer chemoprevention. The precise mechanisms whereby COX-2 inhibitors may prevent cancer development are incompletely understood, but likely include: (1) reduction in arachidonic acid products, (2) prevention of free radical-induced genetic damage, (3) interference with the metabolic activation of carcinogens, (4) reduction of proliferation, (5) induction of apoptosis (i.e., restoration of growth regulation in transformed malignant cells), (6)- immune-stimulation, and (7) anti-angiogenic effects⁴.

COX-inhibitors provide a paradigm for mechanistically-based chemopreventive agent development. Five complementary lines of research have established COX-2 as an important target for preventive intervention: (1) COX-2 is commonly overexpressed in human precancers and cancers; (2) induction of COX-2 stimulates carcinogenesis in preclinical models⁵; (3) COX inhibitors - and COX-2 gene deletions⁶ - inhibit intestinal carcinogenesis in both carcinogen-induced and genetically induced animal models (documented in more than 90 peer-reviewed scientific publications); (4) non-selective COX inhibitors reduce the incidence of colorectal adenomas, cancer, and cancer-associated mortality in human observational studies, (5) COX inhibitors regress pre-cancerous lesions (i.e., aberrant crypt foci and adenomas) in genetic and sporadic colorectal neoplasia cohorts (reported in more than fifteen uncontrolled and controlled studies)⁷. More limited epidemiologic data confirm protective effects of NSAIDs in other cancers, particularly of the stomach and esophagus.

Recently, the field of cancer chemoprevention was invigorated by the success of a randomized, placebo-controlled trial sponsored by the NCI, Pharmacia, and Pfizer^{8,9}. This clinical trial tested a selective COX-2 inhibitor (celecoxib) in 83 persons with FAP, and showed that a 6-month intervention with 400 mg twice a day significantly reduced polyp number within well-defined areas by 28%, with 53% of treated subjects showing $\geq 25\%$ reduction. Significant improvement was also seen in the global colorectal and duodenal polyp status. These findings were presented to the FDA Oncology Drug Advisory Committee in December 1999 and celecoxib was subsequently approved to reduce the number of colorectal adenomas in persons with FAP, in conjunction with usual surveillance and surgical prophylaxis; it has since been approved for use in several other countries as well.

This single trial was significant for several reasons: (1) it provided a complementary treatment option for the colorectal adenoma burden of FAP patients; (2) it prompted additional research in this high-risk cohort; (3) it offered a measure of validation for mechanism-based approaches to clinical chemoprevention; (4) it prompted consideration of non-cancer endpoints for drug approval in cancer prevention; (5) it served as an example of efficient prevention trial design; (6) it provided a scientific rationale and biologically-active dose for testing celecoxib in other cancer prevention settings, especially against sporadic colorectal neoplasia. Follow-up studies have been initiated to assess the relative effects of celecoxib in other FAP settings, including phenotypic suppression and adenoma regression in combination with other chemopreventive agents,

such as difluoromethylornithine (DFMO). Five preclinical studies have demonstrated that the combination of a COX inhibitor and DFMO results in striking reductions in colorectal neoplasia. The long-term goals of chemoprevention in FAP - to reduce cancer risk and/or improve quality of life - as demonstrated by declines in the frequency of invasive surveillance procedures, surgical resections, neoplasia incidence, and cancer-related deaths - have yet to be achieved. Nevertheless, mechanism-based prevention offers significant promise for persons with FAP, and possibly, for others as well. Additional trials of celecoxib involving persons with hereditary non-polyposis colorectal cancer (HNPCC) and others at risk for colorectal carcinoma due to prior adenomas, are ongoing.

While initial prevention studies of COX inhibitors focused on the colon, this class of agents has demonstrated pre-clinical preventive efficacy in several other extra-colonic tissues as well - particularly skin, bladder, aerodigestive, and mammary tumors¹⁰⁻¹⁴. These data, coupled with evidence of COX-2 over-expression during carcinogenesis in a wide range of target organs, further support testing of COX-2 inhibitors in extra-colonic preventive settings. More specifically, the premise for COX-2 inhibitors in esophageal cancer prevention was recently strengthened by data suggesting that MF-Tricyclic reduced inflammation, COX-2 activity, and adenocarcinoma incidence in a rat model of Barrett's-associated neoplasia¹⁵. In addition, the Stanford group recently demonstrated that rofecoxib given over 10 days (25 mg/day orally) reduced COX-2 expression by 77%, reduced mucosal PGE2 content by 59%, and reduced cellular proliferation by 62.5% in patients with Barrett's esophagus¹⁶. The NCI is currently exploring the chemopreventive efficacy of COX-2 inhibitors in esophagus, bladder, skin, prostate, and breast phase II/III clinical trials.

COX-2 inhibitors may play a significant role in cancer treatment as well. For example, Lundholm, et al., described improved survival in patients with metastatic solid tumors treated with indomethacin in the mid-1990's¹⁷. More recently, COX-2 inhibitors have shown promise in cancer therapeutic settings in preclinical models; clinical trials to evaluate these effects are ongoing.

COX inhibitors offer several potential benefits including analgesia, cardiovascular prevention, and possibly preventive effects in cancer and cognitive disorders (e.g., Alzheimer's disease). Learning how to use NSAIDs, COX-2 selective inhibitors, or both optimally in persons at risk for these common diseases will be a challenging, though extremely rewarding, exercise. COX-2 inhibitors currently being tested in preclinical or clinical settings - based on a query of public databases - include CDDO, LM 4108 and Ursolic acid

(Nonindustrial sources); Celecoxib, SC 236, and SC 58125 (Searle); JTE 522 (Japan Tobacco); Meloxicam (Boehringer Ingelheim), Nabumetone (SmithKline Beecham), Nimesulide (Helsinn), NS 398 (Cayman Chemical, Taisho Pharmaceutical), P 54 (Phytochemindo Reksa), and Rofecoxib (Merck & Co).

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The role of FDG-PET in the study of gastro-intestinal tumours.

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INTRODUCTION

Positron emission tomography (PET) allows the in vivo study of tumor metabolism based on its unique potential to measure the tumoral uptake and metabolism of specifically designed radiotracers. Several positron labeled probes have successfully been used for the study of specific aspects of tumor metabolism using PET, such as amino acid uptake (^{11}C -methionine), oxidative metabolism (^{11}C -acetate), protein synthesis (^{11}C -tyrosine) or DNA synthesis and cell proliferation (^{11}C -thymidine). The tracer most commonly used worldwide is fluorine-18-labeled 2-fluoro-2-deoxy-D-glucose (FDG). This is a D-glucose molecule in which a hydroxyl group in the 2-position is replaced by an ^{18}F -label. The use of FDG for in vivo cancer imaging is based upon the presence of enhanced glucose metabolism in cancer cells, which was first described by Warburg several decades ago. After malignant transformation, cells demonstrate an increased expression of the epithelial glucose transporter proteins and an increase in the activity of the principal enzymes of the glycolytic pathway. After intravenous administration, FDG competes with plasma glucose for the glucose transporters in the cell membrane. Because FDG lacks a hydroxyl group in the two position, its first metabolite, FDG-6-phosphate, is not a substrate for the glucosephosphate isomerase, and therefore cannot be converted to the fructose analog. As most tumors have a low phosphatase activity, the negatively charged FDG-6-phosphate will accumulate intracellularly, resulting in a so-called 'metabolic trapping'. Under steady state conditions, the amount of FDG-6-phosphate accumulated is proportional to the rate of glucose utilization. PET yields data independently from associated structural characteristics, and therefore allows the detection or monitoring of biochemical perturbations which are not yet associated with specific structural changes. Moreover, with one injection and in one examination session PET allows the examination of the whole body, which is a major advantage compared to the conventional diagnostic modalities with their inherent field-of-view limitations. In this talk, the clinical value of PET in oesophageal and colorectal cancer will be discussed based on the experience we gained in our hospital.

I. POSITRON EMISSION TOMOGRAPHY IN OESOPHAGEAL CANCER

Staging of Oesophageal cancer

Pretreatment assessment and classification of disease extent is essential in the management of oesophageal cancer. The tumour stage is the major determinant of prognosis and provides the basis for selection of the most appropriate therapeutic strategy. Therefore, a prospective study was designed to compare the staging accuracy of FDG-PET to the standard combined use of CT and EUS. Seventy-four patients with carcinomas of the oesophagus (n=43) or gastro-oesophageal junction (n=31) were studied. All patients underwent attenuation corrected FDG-PET imaging, a spiral CT scan, and an EUS. FDG-PET demonstrated increased activity in the primary tumour in 70/74 patients (sensitivity: 95%). False-negative PET images were found in 4 patients with T1 lesions. FDG-PET had a higher accuracy for diagnosis stage IV disease compared to the combination of CT and EUS. FDG-PET had additional diagnostic value in 16/74 patients (22%) by upstaging 11 (15%) and downstaging 5 (7%) patients. Thirty-nine of the 74 patients (53%) underwent a 2- or 3-field lymphadenectomy in conjunction with primary curative oesophagectomy. In these patients tumoural involvement was found in 21 local and 35 regional or distant LN. For local LN, the sensitivity of FDG-PET was lower than EUS. For the assessment of regional and distant LN involvement, FDG-PET had a higher specificity and a similar sensitivity compared to the combined use of CT and EUS. It was concluded that: 1) PET significantly improves the detection of stage IV disease in EC compared to the conventional staging modalities; and, 2) PET improves diagnostic specificity of LN staging. Based on these study results the authors state that preoperative FDG-PET should be routinely used in patients in whom the standard staging algorithm (i.e. CT scan followed by an EUS) suggests resectable disease. In this patient subset FDG-PET should improve the detection of metastatic disease (Stage IV), and increase the specificity of LN staging.

Staging of Recurrent Oesophageal cancer

Forty-one patients with a clinical or radiological suspicion of recurrent disease underwent conventional diagnostic workup (CDW), including a spiral CT and an EUS and a dedicated whole-body FDG-PET. The CDW and PET findings were correlated with pathology, or radiological and clinical follow-up. Forty recurrences were found in 33 patients. The lesions were located peri-anastomotal (n=9), regional (n=12), and at

distant sites (n=19). For the diagnosis of a peri-anastomotic recurrence, the sensitivity, specificity and accuracy of FDG-PET were 100%, 57% and 74%, versus 100%, 93% and 96% for CDW, respectively. False-positive PET lesions were found in patients with a progressive anastomotic stenosis requiring repetitive endoscopic dilatation. For the diagnosis of a regional and distant recurrence, the sensitivity, specificity and accuracy of PET were 94%, 82% and 87%, versus 81%, 82% and 81% (p=0.08) for CDW. On a patient-base, PET provided additional information in 27% of the patients: a major impact on diagnosis was found in 5 patients with equivocal or negative CDW findings in whom PET provided a true-positive diagnosis. Five other patients were upstaged from localized to extended recurrent disease; and in one patient with an equivocal CDW lesion, PET correctly excluded malignancy. It was concluded that FDG-PET allows a highly sensitive diagnosis and accurate whole-body staging of symptomatic recurrent EC. Further studies in asymptomatic patients are needed to assess the potential benefit on survival.

Evaluation of induction chemoradiation locally advanced oesophageal cancer

Endoscopic ultrasound and computed tomography are inaccurate for assessing response to CRT because of poor differentiation between postchemoradiation fibrosis or inflammation from residual tumour. This prospective study was designed to determine the utility of whole-body FDG-PET for this indication.

Thirty-seven patients with advanced oesophageal cancer (clinical T4 stage without evidence of organ metastases), underwent a whole-body dedicated FDG-PET before and one month after neoadjuvant CRT (40 Gy, 5-FU and cisplatinum). Patients were classified as PET-responders when the post CRT PET demonstrated a strong reduction of FDG uptake at the primary tumour site (> 80% reduction of tumour-to-liver uptake ratio compared to the baseline FDG-PET) without any abnormal FDG uptake elsewhere in the body. The gold standard for response was available in 36 patients based on pathology obtained during surgery (n=30) and by guided biopsy or dedicated radiology in case of a suspicion of progressive disease (n=6).

Fourteen of 36 patients (39%) demonstrated a good pathologic response: pT0-2N0M0 (n=10), and pT3N0M0 with extensive CRT effect on pathology (n=4). Six of these patients (17%) had a pathological complete response (pT0N0M0).

We found a strong correlation between the presence and extent of lymph node involvement as shown by preCRT PET and the response rate of patients treated with neoadjuvant CRT. If only preCRT PET was considered as the staging modality, a major CRT response occurred in 9/11 (82%) N0M0

patients, in 3/9 (33%) N1M0 patients, and in only 2/16 (13%) patients with distant lymphatic spread (M+ly). In line of this, pathologic complete responses (pT0N0M0) were found in 5/11 (45%) N0M0 patients, in only 1/9 (4%) N1M0 patients, and in none of the 16 M+ly patients.

Importantly, this correlation between preCRT disease extent and response rate was not found using CT or EUS as the staging modality.

The overall accuracy of FDG-PET for predicting response was 28/36 (78%). PET was not accurate to diagnose complete pathologic response (sensitivity: 67%, positive predictive value: 50%). The sensitivity of FDG-PET for a major CRT response was 10/14 (71%), and for a CRT non-response 18/22 (82%). The median survival time after CRT of PET responders versus PET non-responders was 16.3 vs 6.4 months (log rank test: p=0.005). Excluding the 8 patients with overt progressive disease who did not undergo surgery, median survival time after CRT was 16.3 and 8.0 months, respectively (log rank test: p=0.01). These data indicate that CRT response as assessed by FDG-PET is strongly correlated with pathologic response and survival.

Future work in this area will test whether FDG-PET performed more early in the CRT course could predict the response and final outcome. This would certainly have a major impact on patient management as well as on the health care resources.

2. POSITRON EMISSION TOMOGRAPHY IN COLORECTAL CANCER

Primary staging of colorectal cancer

FDG-PET depicts all primary colorectal adenocarcinomas. However, the specificity of PET is poor due to the variable physiological intestinal FDG uptake, and to false-positive FDG-uptake in inflammatory bowel conditions and benign adenomata. The ability of FDG-PET for depicting regional lymph node metastasis is poor (sensitivity 29%, specificity 96%). The reasons for this high false-negativity rate of FDG-PET is that the majority of these lymph nodes are located in the immediate vicinity of the primary tumour, and that some of these nodes have histologically only limited, micrometastatic invasion. There are no reports of studies that focussed on the use of whole-body FDG-PET in comparison to state of the art conventional imaging modalities for the detection of distant metastatic (Stage IV) disease in a preoperative setting. In conclusion, there are no data to support the routine use of FDG-PET for preoperative TNM staging of colorectal cancer at the initial diagnosis.

Laparoscopia y cáncer colorrectal

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Los avances tecnológicos han permitido que la cirugía laparoscópica se aplique de forma progresiva al tratamiento de patología colorrectal, tanto benigna como maligna. Sin embargo, la aceptación del tratamiento laparoscópico en patología colorrectal no se ha producido de forma tan rápida como en otras patologías intra abdominales quirúrgicas y sigue siendo motivo de controversia, tanto desde el punto de vista técnico como conceptual. Además, la resección colónica plantea una serie de diferencias técnicas respecto a otras intervenciones como son: la ligadura de estructuras vasculares mayores que en el caso de patología neoplásica será en el origen, tras la resección de la pieza quirúrgica es necesaria la realización de una anastomosis sin tensión y bien vascularizada y además es necesario extraer una pieza quirúrgica, que puede ser voluminosa, intacta para su estudio anatomopatológico, siendo necesaria la realización de una incisión de asistencia. Pero sin duda, la diferencia más importante es que la mayor parte de patología colorrectal que recibe el cirujano digestivo es patología neoplásica y ésta continua siendo actualmente una indicación controvertida para la aplicación de las técnicas laparoscópicas.

En la literatura se han publicado numerosas series prospectivas más o menos largas que comparan la colectomía laparoscópica frente a la colectomía realizada por técnicas convencionales, han demostrado que la cirugía colorrectal por técnicas de laparoscopia es técnicamente posible y segura y que, como ya se ha demostrado en otros procedimientos quirúrgicos, presenta una serie de ventajas en el periodo postoperatorio caracterizadas por una rápida recuperación del paciente y una disminución del periodo de convalecencia. Esto creó una situación de excesivo optimismo que contribuyó a que numerosos cirujanos optaran por la utilización de esta nueva técnica quirúrgica en el tratamiento de patología colorrectal, incluyendo patología maligna. Sin embargo, la publicación de un aumento alarmante en la incidencia de implantes metastásicos en las puertas de entrada de pacientes sometidos a cirugía laparoscópica para el tratamiento de patología neoplásica, incluso en tumores en estadios iniciales, hizo que esta postura inicial de euforia se frenase, muchos cirujanos abandonaron la laparoscopia en el tratamiento de la patología neoplásica, numerosos autores y sociedades quirúrgicas aconsejaron limitar la realización de la cirugía laparoscópica en el cáncer de colon en el contexto de estudios controlados que

realizasen un seguimiento prolongado de los pacientes y se publicaron trabajos que hacían reflexionar sobre la honestidad del cirujano al justificar la utilización de la cirugía laparoscópica en el tratamiento del cáncer basándose tan sólo en las ventajas a corto plazo que esta técnica quirúrgica representaba para el paciente sin saber con exactitud cuál iba a ser la influencia sobre recidiva y supervivencia a largo plazo, sin duda lo más importante cuando hablamos de patología neoplásica.

Se intentarán exponer los diferentes puntos controvertidos que plantea la colectomía laparoscópica en el tratamiento de la enfermedad neoplásica colorrectal: las indicaciones en el cáncer de colon y recto, la resección oncológica, la localización de pequeños tumores intraluminales que pueden pasar desapercibidos y los resultados clínicos de que disponemos hasta el momento actual tanto a corto plazo como en cuanto a supervivencia y recidiva a largo plazo.

1.INDICACIONES DE LA CIRUGÍA LAPAROSCÓPICA EN EL CÁNCER COLORRECTAL

Las indicaciones de la cirugía colorrectal por laparoscopia se van modificando a medida que la tecnología y la experiencia de los grupos quirúrgicos avanzan. En un principio sólo se indicaban en mínimas resecciones colónicas segmentarias o como tratamiento paliativo en pacientes en estadios avanzados de la enfermedad, pero actualmente pueden realizarse todas las intervenciones colorrectales por técnicas laparoscópicas.

Aunque está aceptado que las indicaciones de la colectomía laparoscópica incluyen prácticamente todas las patologías colorrectales benignas, siendo la única limitación para su realización la experiencia del cirujano, la indicación de la laparoscopia en el tratamiento del cáncer colorrectal es aún un tema de controversia y aunque muchos trabajos han demostrado es técnicamente posible y oncológicamente segura, la mayoría de cirujanos creen que la indicación de la cirugía laparoscópica en neoplasia de colon curable debe limitarse aún a centros en los que se realicen estudios controlados. Tampoco existe unanimidad en cual es el paciente ideal para realizar la resección del colon por laparoscopia, inicialmente se consideró que el paciente en estadio avanzado sería el candidato ideal, ya que no se influiría en la supervivencia global, actualmente el desarrollo de terapias complementarias nos permite ofrecer a estos pacientes la posibilidad de mejorar la supervivencia y por tanto la resección del colon debe ser tan oncológica como en pacientes en estadios iniciales. Por tanto, debemos tener en cuenta que la selección de pacientes es tan

importante en cirugía laparoscópica como en cirugía convencional, pues, *“un paciente que no es un buen candidato para una intervención de cirugía convencional no es un candidato apropiado para cirugía laparoscópica”*, es decir las indicaciones en cirugía laparoscópica deben ser idénticas a las de la cirugía convencional.

Existen una serie de situaciones que son consideradas contraindicaciones de la colectomía laparoscópica, las cuales podemos dividir en absolutas y relativas, dependiendo estas últimas de la experiencia del cirujano (Tabla 1). Debemos considerar contraindicaciones relativa que merece especial mención, para la realización de laparoscopia la existencia de una neoplasia exteriorizada o que infiltre órganos adyacentes (Estadio T4) pues, la manipulación tumoral será mayor, existiendo un mayor riesgo de liberación de células neoplásicas y de diseminación por efecto del CO₂. Otras contraindicaciones relativas son específicas en cuanto a la localización del tumor, debido a la mayor dificultad técnica que estas resecciones quirúrgicas conllevan.

2. RESECCIÓN ONCOLÓGICA

En cirugía colorrectal por laparoscopia deben preservarse los principios fundamentales de la cirugía en esta área. En primer lugar, deben hacerse una serie de consideraciones dependiendo del tipo de patología a la que se aplique esta técnica. En el tratamiento de patología colorrectal neoplásica, es fundamental seguir rigurosamente las bases de una resección oncológica. Uno de los puntos “criticados” por los detractores de la cirugía laparoscópica en el tratamiento de patología colorrectal maligna es que este tipo de cirugía no puede garantizar una resección oncológica.

Toda resección colónica en el tratamiento de patología rectal tanto por técnicas de cirugía laparoscópica como por cirugía convencional, debe realizarse siguiendo unos principios oncológicos: resección en bloque del segmento colónico con el territorio ganglionar correspondiente, evitar la manipulación del tumor (técnica del “non-touch”), márgenes libres suficientes y ligadura de los vasos en el origen.

Inicialmente existían dudas sobre si la calidad de la resección era la misma cuando se realizaba por vía laparoscópica que por convencional, ya en 1993 Monson et al. publicaron que una de las ventajas de la técnica laparoscópica era que la laparoscopia permitía *“una incomparable visión..., permitiendo una cuidadosa resección radical... completamente bajo visión directa”*, por lo que esta técnica quirúrgica permitirá realizar una disección cuidadosa y una resección extensa.

Para determinar si la resección realizada por laparoscopia es igual de efectiva que la realizada por cirugía convencional en la mayoría de estudios publicados, se ha realizado un estudio anatomopatológico de la pieza quirúrgica en el cual se han valorado: la longitud del segmento colónico resecado, la distancia existente entre el tumor y los márgenes de resección y la identificación exhaustiva del número de adenopatías incluidas en la pieza quirúrgica. La valoración del número de ganglios resecados, sin embargo, presenta una serie de inconvenientes, ya que éste varía de forma considerable dependiendo del segmento de intestino que se extirpa, de la localización del tumor primario y del esfuerzo del patólogo en la identificación de los ganglios, para evitar este sesgo, es conveniente que sea el mismo patólogo el que examine las piezas quirúrgicas. Asimismo, numerosos autores han demostrado que el número de ganglios linfáticos resecados, la longitud del segmento colorrectal extirpado y el margen de resección distal, son iguales con ambas técnicas quirúrgicas (convencional vs. laparoscopia) (Tabla 2).

3. LOCALIZACIÓN INTRAOPERATORIA DE TUMORES

Uno de los problemas que se plantean para el tratamiento de pequeñas lesiones tumorales intraluminales colorrectales es su localización durante la exploración laparoscópica, debido a la imposibilidad de palpar el intestino, por la falta de sensación táctil del cirujano.

Para intentar solventar este problema se han propuesto diferentes técnicas, una de ellas es la tinción preoperatoria con tinta china, índigo carmín, verde de indocianina, azul de metileno o algún otro colorante de la lesión. Estos colorantes dejarán un tatuaje en la pared del colon que permitirá su visualización e identificación durante la cirugía laparoscópica.

Otra opción técnica que puede utilizarse para la identificación de pequeñas lesiones intraluminales es la realización de una colonoscopia intraoperatoria. Debe tenerse en cuenta que si el aire insuflado es excesivo, causa una pérdida de espacio de trabajo y dificulta la movilización intestinal, por tanto antes de insertar el endoscopio flexible, debe ocluirse el íleon distal o colon proximal mediante clamps atraumáticos. Una vez localizada la lesión se procede a marcar la pared intestinal mediante puntos de sutura o clips metálicos. El inconveniente es que la cicatriz del pólipo extirpado desaparece entre las 3-8 semanas tras la extirpación, por lo que si la cirugía se retrasa la fibrocolonoscopia intraoperatoria no podrá localizar la lesión.

También se ha realizado marcaje preoperatorio endoscópico de la lesión con clips metálicos y posterior localización intraoperatoria de éstos con fluoroscopia o mediante ecografía intraoperatoria.

4. RESULTADOS A CORTO PLAZO EN LA COLECTOMÍA LAPAROSCÓPICA

Los resultados publicados por la mayoría de autores demuestran que la resección del colon por laparoscopia presenta una serie de ventajas en comparación a las técnicas de cirugía convencional. Estas ventajas, ya demostradas para el tratamiento quirúrgico laparoscópico de patología intraabdominal menor, incluyen menor dolor postoperatorio, recuperación inmediata de la motilidad intestinal con desaparición del íleo postoperatorio y menor número de complicaciones postoperatorias, lo que conlleva a una reducción de la estancia hospitalaria y a una más rápida recuperación de la actividad habitual del paciente. Sin embargo, en la colecistectomía convencional la incisión cutánea representa la mayor parte del trauma quirúrgico, por lo que cuando la intervención se realiza por laparoscopia, se produce una gran reducción en la agresión quirúrgica y los beneficios en términos de recuperación a corto plazo son inmediatamente evidentes. En las resecciones colorrectales, la incisión cutánea, aunque sin duda importante, representa tan solo una pequeña parte del traumatismo quirúrgico total, el cual incluirá la manipulación de varios cuadrantes abdominales, la movilización del paquete intestinal, la disección ganglionar y la realización de una anastomosis intestinal, entre otras. Por tanto, cuando la intervención se realiza asistida por laparoscopia, la reducción de la incisión cutánea (ya que la agresión quirúrgica intraabdominal es la misma por ambas técnicas quirúrgicas) no hace pensar que este tipo de cirugía vaya a representar muchos beneficios respecto a la cirugía convencional y por ende que la influencia en la recuperación del paciente y la menor aparición de complicaciones postoperatorias no serán tan evidentes. Existen estudios que comparan la colectomía laparoscópica con la convencional y que no han encontrado diferencias en los resultados a corto plazo entre ambas técnicas quirúrgicas, aunque la gran mayoría de series prospectivas publicadas, si evidencian una recuperación a corto plazo más favorable en los pacientes intervenidos por técnicas laparoscópicas. Además, diferentes series han demostrado que la cirugía colorrectal por laparoscopia presenta unas desventajas respecto a la colectomía convencional como son la mayor duración de la intervención quirúrgica, (relacionado con la mayor dificultad técnica que implica este tipo de intervenciones y con una curva de aprendizaje más prolongada), el mayor índice de conversión y un mayor coste económico.

La cirugía colorrectal presenta una serie de diferencias respecto a otras intervenciones intraabdominales que la hacen técnicamente más compleja y por tanto, la curva de aprendizaje necesaria será más prolongada. La duración de la curva de aprendizaje en la colectomía laparoscópica no está bien definida y en la literatura, aunque se han publicado estudios que han intentado definirla, el número de casos necesarios para

conseguir la curva de aprendizaje es muy variable entre ellos y oscila entre 11 y 70 resecciones de colon, según las series.

Las diferentes series prospectivas publicadas han demostrado que los resultados obtenidos en la cirugía laparoscópica pueden variar a medida que aumenta la experiencia, con tiempos operatorios que disminuyen de forma significativa a medida que aumenta el número de casos intervenidos, disminución del índice de conversión, disminución del número de complicaciones intra y postoperatorias, y en consecuencia, con acortamiento de la estancia hospitalaria (Tabla 3).

Las tasas de conversión publicadas en la literatura son variables, oscilando según las series entre el 14 y el 22 %, aunque existen series que publican cifras más altas de hasta el 40%. En un estudio multicéntrico de la American Society of Colon and Rectal Surgeons que incluía 114 cirujanos, la tasa media de conversión fue del 22,8%, variando entre el 33,5% en el caso de resecciones rectales hasta el 16% en las hemicolectomía derechas. Las causas más frecuentes de conversión son la presencia de adherencias en pacientes con antecedentes quirúrgicos previos, la hemorragia intraoperatoria que impide la correcta visualización del campo quirúrgico y en el caso de patología neoplásica la existencia de grandes tumores con infiltración local, en estos casos, intraoperatoriamente es difícil diferenciar el tejido neoplásico de la reacción inflamatoria peritumoral y el riesgo que supone la manipulación de la tumoración, justifica la realización de una laparotomía, ya que la manipulación de tejido tumoral podría provocar la liberación de células neoplásicas que pueden diseminarse por efecto del CO₂ y posteriormente favorecer la aparición de implantes.

En la mayoría de estudios comparativos publicados el tiempo operatorio es significativamente mayor en los pacientes intervenidos por cirugía laparoscópica, variando el tiempo medio de intervención entre 160 a 348 minutos, según el tipo de resección realizada. Pero a medida que se adquiere experiencia el tiempo operatorio disminuye, reduciéndose en la mayoría de las series hasta una media de 190 minutos e incluso desapareciendo las diferencias cuando se compara con pacientes intervenidos por técnicas convencionales. En un estudio que compara 102 resecciones colónicas por laparoscopia con una serie histórica de 705 resecciones colónicas abiertas, el tiempo operatorio en resecciones derechas e izquierdas fueron similares entre ambos grupos (150 min. vs 144 min. en la hemicolectomía derecha y 204 min. vs 209 min. en la colectomía izquierda, por laparoscopia y cirugía convencional respectivamente), aunque en este estudio no se especifica la experiencia ni el número de cirujanos que intervienen en el estudio.

En las diferentes series publicadas se demuestra una reducción significativa del íleo postoperatorio y un inicio más precoz de la ingesta tras colectomía laparoscópica que tras colectomía convencional. Ello se debe, probablemente, a una menor manipulación intestinal, al mejor mantenimiento de las condiciones intraabdominales de temperatura y humedad, a una respuesta hormonal diferente y a la administración de menos analgésicos derivados de la morfina, todo ello, junto a la deambulación precoz del paciente. Este restablecimiento más precoz del peristaltismo intestinal y la práctica desaparición del íleo postoperatorio ha permitido el inicio precoz de la ingesta en los pacientes intervenidos por técnicas laparoscópicas. Asimismo, hemos asistido a un cambio de actitud que ha incluido a los pacientes sometidos a cirugía convencional, ya que antes de la introducción de las técnicas laparoscópicas, el inicio de la dieta oral se condicionaba no sólo al inicio del peristaltismo, sino que tradicionalmente se retrasaba hasta que el paciente había realizado deposiciones.

Otra de las ventajas clínicas que se han observado en los pacientes sometidos a cirugía laparoscópica es la menor incidencia de complicaciones postoperatorias, principalmente complicaciones infecciosas, tal como se desprende del análisis de series amplias de pacientes intervenidos por laparoscopia. Existen estudios prospectivos que demuestran una menor morbilidad postoperatoria tras colectomía laparoscópica que tras colectomía convencional, sin embargo, existen otros trabajos que no demuestran beneficios en la colectomía laparoscópica en comparación con la colectomía convencional e incluso algunos grupos publican mayores tasas de complicaciones postoperatorias tras cirugía laparoscópica del colon.

Otra de las desventajas de la laparoscopia en el tratamiento de la patología colorrectal es que ésta puede suponer un coste económico superior que la cirugía convencional, debido, principalmente al mayor gasto intraoperatorio que supone esta técnica quirúrgica y que se relaciona directamente con un tiempo quirúrgico más prolongado y con la utilización de mayor cantidad de material desechable. Sin embargo, con la cirugía laparoscópica el coste económico durante el ingreso postoperatorio del paciente es menor y esto estaría relacionado con la rápida recuperación del paciente y en consecuencia, con la reducción de la estancia hospitalaria. Por tanto, si la laparoscopia reduce o no el coste total, depende del balance entre dos grupos de factores opuestos: los que aumentan los costes de quirófano y los que disminuyen los costes hospitalarios. Además, las ventajas reales de la colectomía laparoscópica pueden ser sólo mejor apreciadas cuando los costes son analizados a más largo plazo, es decir, valorando el tiempo que el paciente tarda en reincorporarse a su actividad habitual. Aunque hasta el momento no hay datos en la literatura que valoren el coste económico de la colectomía laparoscópica

incluyendo el periodo de baja laboral, posiblemente debido a que en la mayoría de series los pacientes intervenidos de cáncer de colon son de edad avanzada y no se incorporarán a una actividad profesional. La mayoría de series publicadas que analizan el coste económico que supone la resección colónica por laparoscopia, revelan que los costes en cirugía laparoscópica y convencional tienden a ser similares. Falk et al. realizaron un análisis de los costes, estratificando los casos según el tipo de intervención realizada, no encontrando diferencias entre ambos tipos de cirugía, principalmente a expensas de una menor estancia hospitalaria en el grupo laparoscópico. Sin embargo, los estudios prospectivos y no aleatorizados de Philipson et al y Bokey et al. que comparan la hemicolectomía derecha y convencional en pacientes intervenidos por cáncer, observan que el coste es significativamente mayor en los pacientes del grupo de cirugía laparoscópica, relacionado con el hecho de que ambos autores no observan diferencias en la incidencia de complicaciones postoperatorias y en la estancia entre ambos grupos.

5. SUPERVIVENCIA Y RECIDIVA EN LA COLECTOMÍA LAPAROSCÓPICA POR CÁNCER DE COLON

El cáncer de colon es una enfermedad que puede ser quirúrgicamente curable en más de un 50% de los casos. Consecuentemente, los beneficios en términos de cosmética, reducción del dolor postoperatorio, disminución de la estancia hospitalaria y más rápida incorporación a la actividad habitual deben ser valorados frente a la posibilidad de reducir las curvas de supervivencia o índices de curabilidad.

Uno de los principales puntos de controversia en el tratamiento de patología neoplásica mediante técnicas de cirugía laparoscópica es la aparición de implantes metastásicos en las cicatrices de los orificios de los trócares, los denominados "port site" metástasis. La alarma se inició cuando se empezaron a publicar implantes en la pared abdominal tras colecistectomía laparoscópica en pacientes con carcinoma de vesícula no sospechado. En 1993, dos años después de la introducción de la laparoscopia en la resección colónica, Alexander et al. publicaron el primer caso tras una colectomía laparoscópica, en una mujer de 67 años intervenida 3 meses antes de una adenocarcinoma de colon derecho en estadio Dukes C. En algunos de los casos publicados existe seguridad de la no-manipulación del tumor durante la cirugía y además este problema no es sólo exclusivo de lesiones en estadios avanzados, ya que se han descrito casos en pacientes con neoplasias en estadios muy iniciales, como tumores de colon en estadio Dukes A, carcinomas de vesícula con invasión sólo de la mucosa y carcinomas in situ. Sin embargo, las metástasis en la pared abdominal tras cirugía convencional aunque es una

forma de recidiva infrecuente, existen, y dos estudios retrospectivos publican una incidencia que se encuentra entre el 0.68-1%. La incidencia de implantes en la pared abdominal tras cirugía laparoscópica en el cáncer de colon, según las series publicadas, oscila entre el 0% y el 4%, existiendo, incluso series que recogen incidencias del 21%. El análisis de 504 casos recogidos en el registro de cáncer de colon intervenidos por laparoscopia de la American Society of Colon and Rectal Surgeons, ha demostrado que en una serie de 480 casos seguidos durante un periodo superior a un año, la incidencia de implantes fue del 1.1% (se detectaron implantes en 5 pacientes, todos ellos en Estadio III según la clasificación TNM). Es decir, parece ser que la incidencia de tumores en las incisiones tras cirugía convencional y laparoscópica en el tratamiento del cáncer colorrectal es similar.

Hasta el momento actual, existe un vacío en cuanto a la publicación de series que incluyan un número importante de pacientes con un seguimiento prolongado y en la publicación de series prospectivas aleatorizadas.

Recientemente, nuestro grupo ha publicado un estudio prospectivo y aleatorizado que compara los resultados a largo plazo de pacientes intervenidos por laparoscopia, con pacientes idénticos intervenidos por técnicas de cirugía convencional, la mediana de seguimiento es superior a 3 años (43 meses), periodo de seguimiento adecuado si se acepta que más del 70% de las recidivas en el cáncer colorrectal aparecen en los dos primeros años de seguimiento y que el 80% de los implantes metastásicos, en los pacientes sometidos a resección laparoscópica, aparecen dentro del primer años de seguimiento. Los resultados del seguimiento a largo plazo han demostrado un claro beneficio de la cirugía laparoscópica respecto a la cirugía convencional en cuanto a la supervivencia relacionada con cáncer. Los pacientes intervenidos por laparoscopia presentan una reducción del 62% en el riesgo de fallecer por el cáncer respecto al grupo de cirugía convencional. Además, el análisis multivariado seleccionó la técnica laparoscópica, junto con la presencia de metástasis ganglionares y los niveles preoperatorios de CEA, con un factor predictivo independiente de recidiva tumoral, supervivencia global y supervivencia relacionada con cáncer. Un aspecto a resaltar en los resultados obtenidos es la superioridad de la cirugía laparoscópica frente a la cirugía convencional en los pacientes con neoplasias en estadio avanzado sin presencia de metástasis (Dukes C y Estadio III). En estos pacientes la cirugía laparoscópica se ha asociado con una menor probabilidad de recidiva, una mejor supervivencia libre de recidiva a los 5 años, una mayor supervivencia global y una mayor supervivencia relacionada con cáncer. Sin embargo, en pacientes en estadios precoces de la enfermedad (Estadios I y II de la clasificación TNM), esas variables han sido idénticas en ambos grupos de tratamiento.

Estos resultados están en concordancia con los publicados recientemente en otras series prospectivas que muestran una supervivencia a largo plazo en pacientes sometidos a resección por cáncer de colon discretamente superior, aunque sin diferencias estadísticamente significativas, a la supervivencia descrita en series históricas de cirugía convencional, en las cuales la supervivencia a los 4 o 5 años de seguimiento se sitúa alrededor del 60%. El grupo de Norfolk presentó los resultados de los primeros 24 meses de seguimiento en 39 pacientes, las muertes relacionadas con cáncer fueron el 6%, con una incidencia global de recidiva del 9%, no apareció ningún implante metastásico en las puertas de entrada y la supervivencia a los 3 años en su serie fue del 92% en pacientes con ganglios negativos y de un 79% en pacientes con ganglios positivos, resultados mejores a los que podrían anticiparse tras cirugía convencional. De forma similar, Franklin et al. compararon los resultados de una serie prospectiva de 191 pacientes intervenidos por laparoscopia con un grupo control de 224 pacientes intervenidos por cirugía convencional por otro grupo de cirujanos, con un seguimiento medio de 30 meses, no hallando diferencias en la supervivencia a largo plazo entre ambos grupos, pero siendo la supervivencia libre de recidiva del 80% en el grupo laparoscópico frente al 67% en el grupo convencional. Hartley et al., en un estudio prospectivo comparando un grupo de 61 pacientes intervenidos de cáncer colorrectal por laparoscopia con un grupo de 53 pacientes intervenidos por técnicas convencionales, no hallaron diferencias, con un seguimiento medio de 42 meses, en la supervivencia global ni en la recidiva entre ambos grupos, no detectando ningún caso de implante metastásico en el grupo laparoscópico. Poulin et al. en un estudio prospectivo sobre 135 pacientes intervenidos de forma consecutiva por cáncer colorrectal, publica con un seguimiento medio de 24 meses, una mejor supervivencia global a los 2 (81%) y 4 (68%) años comparándola con series históricas de cirugía convencional, sin detectar ningún caso de implante metastásico en las puertas de entrada, sugiriendo con los resultados obtenidos, la posibilidad que la laparoscopia influya positivamente en el seguimiento a largo plazo, con una disminución de la tasa de mortalidad y una mejoría en la supervivencia de los pacientes en cualquier estadio de la enfermedad.

El cirujano puede ser un factor relevante en la supervivencia del cáncer colorrectal. Existen estudios que demuestran que los cirujanos con especial dedicación a la patología colorrectal y por tanto, que realizan un elevado número de intervenciones de cirugía colorrectal, obtienen unos mejores resultados en la supervivencia de pacientes intervenidos de cáncer colorrectal. Esta experiencia y los mejores resultados demostrados en la cirugía convencional, pueden ser, incluso más relevantes, en la cirugía laparoscópica que necesita un entrenamiento específico. Otros posibles factores que pueden influir en la

supervivencia de los pacientes intervenidos de cáncer de colon por técnicas laparoscópicas del grupo laparoscópico pueden estar relacionados con la inmunosupresión postoperatoria inducida por la cirugía. Se ha demostrado, en estudios clínicos y experimentales, que la cirugía produce un periodo de relativa inmunosupresión, cuya intensidad y duración es proporcional a la severidad de la agresión. Este estado de inmunodepresión induce a alteraciones que pueden estar implicadas en el desarrollo de complicaciones sépticas y, lo más importante, en la aparición de metástasis tumorales. Se han publicado numerosos estudios que han demostrado una menor inmunosupresión postoperatoria inducida por la cirugía laparoscópica en comparación con la cirugía convencional, pero el posible impacto en la supervivencia a largo plazo de los pacientes intervenidos por cáncer es aún desconocida.

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TABLAS

Tabla 1.

Contraindicaciones de la cirugía laparoscópica

RELATIVAS	ABSOLUTAS
- Cirugía abdominal previa	- Oclusión intestinal
- Obesidad mórbida	
- Embarazo	
- Trastornos coagulación	
- Patología cardiopulmonar severa	
- Tumores colon transversos y ángulo esplénico	
- Neoplasia exteriorizada (T4)	

Tabla 2.

Número de ganglios extirpados en la colectomía laparoscópica vs convencional.

REFERENCIA.	AÑO	Nº (CL / CC)	TIPO INTERVENCIÓN QUIRÚRGICA	Nº GANGLIOS	
				CL	CC
Hoffman.	1994	32/31	Colon y recto	8.0	6.1
Musser et al	1994	17/24	Colon y recto	10.6	7.9
Van Ye et al.	1994	14/20	Colon y recto	10.5	7.6
Tucker et al.	1995	20/15	Colon y recto	8.7	6.4
Saba et al.	1995	20/25	Colon	6	10
Franklin et al.	1996	194/214	Colon y recto	37	32
Lord et al.	1996	13/19	Colon derecho Recto	11.6 7.8	10.1 8.9
Stage et al.	1997	15/14	Colon y recto	7	8
Bouvet et al.	1998	53/57	Colon y recto	8	10
Lezoche et al.	2000	150/160	Colon y recto	10.3	8.9
Lacy et al.	2002	111/108	Colon	7.9	7.4

Tabla 3.

Curva de aprendizaje. Relación entre el número de colectomías laparoscópicas y el seguimiento.

REFERENCIA	Nº CASOS	CONVERSIÓN	COMPLIC. INTRAOP.	COMPLIC. POSTOP.	Tº IQ (MIN)	ESTANCIA (DIAS)
Bennet et al.	< 40	25.5%	6.3%	18.6%	-	6
	> 40	25.1%	3.7%	9.9%	-	6
Wishner et al.	< 50	25%	-	-	215	6.4
	> 50	20%	-	-	143	5.5
Senagore et al.	< 40	32%	-	-	185	7
	> 40	10%	-	-	165	4
Reissman et al.	< 33	9%	-	42%	-	-
	33-66	3%	-27%	-	-	-
	> 66	9%	-	12%	-	-
Agachan et al.	< 70	21.5%	29%	32.5%	190	8.2
	> 70	23%	7.3%	14.3%	141	6.6
Lezoche et al	< 50	19.3%	-	-	295	-
	> 50	4%	-	-	200	-

En negrita diferencias estadísticamente significativas.

Eficacia en el tratamiento del cáncer colorrectal avanzado.

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El cáncer colorrectal ocupa el tercer lugar en frecuencia en el hombre y el segundo en la mujer. Es la cuarta causa de mortalidad por cáncer en los países occidentales por lo que representa un importante problema de salud pública. Si tenemos en cuenta que más del 50% de los pacientes con cáncer colorrectal tendrán enfermedad metastásica o localmente avanzada irreseccable en algún momento de la evolución de la enfermedad, el tratamiento sistémico adquiere un importante papel en la estrategia terapéutica de ésta neoplasia.

Tras el empleo de múltiples fármacos y combinaciones el 5-Fluorouracilo se situó en la década de los 70 como el fármaco más activo, y hoy día, tras haber potenciado su eficacia con la modulación bioquímica y con la infusión continua, sigue siendo en combinación, el citostático de elección en primera línea de tratamiento. Ya no es discutible el beneficio de la quimioterapia en el cáncer de colon metastásico o avanzado. El dilema actual estriba en decidir cuál es el mejor tratamiento quimioterápico que puede recibir un paciente en base a las características que presenta, ya sea inherente a la neoplasia o al propio paciente.

Un mejor conocimiento de la biología de la célula tumoral, ha permitido el desarrollo de nuevos citotóxicos activos en el carcinoma colorrectal con algunos de ellos con mecanismos de acción similar al 5FU (raltitrexed y capecitabina) y otros con mecanismos completamente diferentes (oxaliplatino e irinotecan), lo que está permitiendo en estos últimos años combinarlos con un espectro de mayor toxicidad, pero con la esperanza de aumentar la tasa de respuestas y sobre todo aumentar la calidad de vida y la supervivencia de nuestros pacientes.

La combinación de citotóxicos es hoy día un concepto que parece incuestionable y necesario en el tratamiento del cáncer, si queremos obtener una mayor capacidad antitumoral con la mínima toxicidad y evitar en la medida de lo posible la formación de resistencias.

El irinotecan es un fármaco inhibidor de la enzima topoisomerasa 1 que ha demostrado actividad tanto en primera y segunda línea de tratamiento del carcinoma de colon, con una tasa de respuesta global de un 17-25%, equiparable a las obtenidas el 5FU modulado.

Los resultados de los estudios fase II realizados hasta el momento son bastante esperanzadores, obteniéndose tasas de respuestas objetivas en segunda y tercera línea de tratamiento que van desde el 15-30%.

Dos estudios fase III han sido definitivos para establecer la asociación de 5-Fluorouracilo e Irinotecan como el esquema de elección en la primera línea de tratamiento del carcinoma colorrectal avanzado. En el primero de ellos (Douillard y col.) se han randomizado 338 pacientes a recibir un esquema con CPT-11 más 5FU infusión continua modulado con ácido folínico, frente al mismo esquema sin CPT-11. El tratamiento se mantiene hasta progresión. Este estudio demuestra que la combinación con CPT-11 supone un incremento estadísticamente significativo en la tasa de respuestas (R.Globales: 41% vs 23%), en el tiempo a la progresión 6,7 meses vs 4,4 meses y también en la supervivencia (17,4 meses vs 14.1 meses). El otro estudio (Saltz y col.) randomiza 457 pacientes a recibir 5-Fluorouracilo bolus más Lederfolin y CPT-11 frente al mismo esquema sin CPT-11, obteniendo de manera significativa mejores tasas de respuesta 39% vs 21%, mejor tiempo a la progresión (7 meses vs 4,3 meses) y mejor supervivencia (14 meses vs 12.9 meses).

El Oxaliplatino (L-OHP) Es un análogo del cisplatino pero con patrones de actividad y toxicidad diferentes. En monoterapia es un fármaco que ha demostrado una actividad similar al 5-FU, con un porcentaje de respuestas objetivas (sin tener en cuenta estabilizaciones) entre el 17-22%. Su mecanismo de acción es diferente del 5FU, no habiéndose demostrado resistencia cruzada; si además tenemos en cuenta que la toxicidad no es superponible y que in vitro se ha demostrado un sinergismo, el oxaliplatino es un fármaco muy interesante para la combinación con 5-FU.

Las respuestas obtenidas van desde el 25% al 58%, con una tasa de respuesta completas del 3,5% al 5% . De forma global el tiempo libre de progresión de 5,8 meses a 11 meses y la supervivencia de 12 a 17 meses la tasa de respuestas es similar en las diferentes localizaciones metastásicas.

Una cuestión fundamental fue conocer si la adición de oxaliplatino incrementaba de forma significativa la tasa de respuestas y la supervivencia con respecto a las que se obtiene con tratamientos con 5FU. Con este objetivo se han realizado dos estudios Fase III europeos . En un primer estudio (Giachetti y col.) se compara un régimen de administración cronomodulada de oxaliplatino más 5FU y ácido folínico con un esquema sin oxaliplatino. Tras inclusión de 100 pacientes con

carcinoma colorrectal metastásico no pretratados en cada rama, la tasa de respuestas (53% vs. 16%) y el tiempo a la progresión (8,7 vs 6,7 meses) fue significativamente mayor en la rama del oxaliplatino; en cuanto a la supervivencia no hubo diferencias (19 vs. 19,9 meses).

En el segundo fase III (De Gramont y col.) realizado, se compara un esquema bisemanal que incluye oxaliplatino, 5FU bolus modulado y 5FU en infusión continua, con el mismo esquema sin oxaliplatino. Incluidos 420 pacientes, de nuevo se confirma una mayor tasa de respuestas (50,7% vs. 22,3%; $p < 0,05$) e intervalo libre de progresión (9 vs. 6,2 meses), a favor de la rama con oxaliplatino.

En este mismo sentido recientemente en ASCO de este año Grothey y col. han presentado un estudio fase III en el que comparan FUFOX con 5-FU+LV (regimen de la Mayo) demostrando con la inclusión de 242 pacientes que FUFOX es más efectivo (48,3% vs 22,6% $p < 0.0001$), tiene mejor tiempo a la progresión (5,3 meses vs 7,9 meses $p < 0.0001$), mejor supervivencia (16,1 meses vs 20,4 meses) y es menos tóxico.

Golberg y col. también en ASCO de este año han presentado los resultados de un estudio fase III (N9741) que si bien se inició con 5 ramas al final compara IFL frente a FOLFOX encontrándose una mayor eficacia a favor del FOLFOX (38% vs 29% $p < 0.03$), mejor tiempo a la progresión $p < 0.0009$ y una mejor supervivencia (14,1 meses vs 18,6 meses $p < 0.002$), fase III que como los mismos autores discuten a comparado 5-FU en ic (FOLFOX) frente a bolus (IFL) y la influencia del rescate en la supervivencia, esto nos muestra el beneficio de los regímenes combinados utilizando oxaliplatino, beneficio ya conocido en gran parte de Europa.

La Capecitabina es un análogo del 5FU diseñado con el objetivo de disminuir la toxicidad digestiva e incrementar la actividad. Tras su absorción es metabolizada a nivel hepático y activada por la timidin fosforilasa presente en mayor concentración en las células tumorales. Su mayor desarrollo clínico se ha producido en el tratamiento del carcinoma de mama. In vivo ha demostrado sinergismo cuando se combina con ciclofosfamida, taxanos y mitomicina. En los últimos años también se está desarrollando en el tratamiento del carcinoma colorrectal. Estudios fase III han demostrado una eficacia superior a esquemas clásicos de 5 Fu bolus modulado.

Se han realizado estudios fase I y II tanto con capecitabina más oxaliplatino (Evans y col.), así como con Irinotecan (Twelves y col.), demostrando su factibilidad y actividad por lo que podría ser una alternativa a la infusión continua de 5-Fluorouracilo. Se ha observado una eficacia similar con ambas combinaciones aunque los resultados son prematuros (37,5% respuesta X+CPT-11 vs 41.2% X+Oxa)(Jordan et al).

Actualmente se han puesto en marcha dos estudios uno internacional con capecitabina más CPT-11 vs. 5-Fluorouracilo infusión continua más CPT-11 y otro en el seno del grupo TTD que compara capecitabina más oxaliplatino más 5-Fluorouracilo más oxaliplatino con el objeto de conocer si realmente la capecitabina desplazará al Fluorouracilo o no.

En otro sentido tenemos que tener en cuenta el mayor conocimiento de la biología molecular que nos está permitiendo conocer factores biológicos que nos pueden predecir el pronóstico, así como la respuesta y toxicidad al tratamiento que vamos a utilizar, (TS, TP, DPD, P53, MSI, etc), lo que nos va a permitir, en un futuro no muy lejano, adecuar el tratamiento que vamos a utilizar a las características moleculares de la célula/as tumorales que tiene cada paciente.

Al mismo tiempo se ha profundizado en la fisiopatología de la célula tumoral y conocemos como hay una autosuficiencia en las señales de crecimiento, una insensibilidad a las señales inhibitorias del crecimiento, una alteración de la muerte celular programada, una capacidad de replicación ilimitada, una angiogénesis mantenida, así como la capacidad de invadir los tejidos y dar metástasis a distancia. Estos conocimientos han hecho posible la detección de nuevas dianas terapéuticas y el diseño de fármacos fundamentalmente citostáticos que van a actuar en las diferentes dianas, de manera que emerge con fuerza la terapia génica como tratamiento en el cáncer intentando: impedir la expresión de los oncogenes, utilizando la p53 como diana terapéutica, aumentando la inmunogenicidad tumoral, utilizando vectores que porten genes suicidas, diseñando terapias antiangiogénicas y sobre todo diseñando terapias combinadas y nuevas estrategias terapéuticas que nos permitirán, sin lugar a dudas seguir avanzando en el tratamiento del cáncer.

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Capecitabine in combination in advanced colorectal cancer.

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INTRODUCTION

Thanks to modern combination chemotherapy regimens, the natural history of advanced colorectal cancer has been changed over the last few years. As a result, it has been possible to increase response rates, time to progression and overall survival, and therefore classify it as a chemosensitive rather than chemoresistant tumour. This combination treatment includes the use of 5-Fluorouracil (5-FU) either as bolus or continuous infusion, concomitantly to Irinotecan (CPT-11) or Oxaliplatin (OXL). A number of studies have shown continuous infusion to be superior to the bolus form of 5-FU, especially in terms of response rate and hematological tolerance, with the continuous infusion 5-FU schedules known as DeGramont, AIO and TTD being the most popular. However, continuous infusion of 5-FU has some limitations because of the frequency of hospital visits, and the need to use infusion pumps and venous access, aspects that undoubtedly reduce patients' convenience.

An interesting alternative is the use of oral fluoropyrimidines, so 5-FU either as bolus form or continuous infusion can be substituted for an oral treatment. The most extensively studied drugs (although not the only ones) have been UFT and Capecitabine, true prodrugs which are converted in vivo into 5-FU. These oral fluoropyrimidines have the advantages of being administered orally, not requiring day hospital, not needing the use of pumps and catheters, and being well tolerated in general. Also, from a pharmacokinetic point of view, these drugs show areas under the curve of 5-FU similar to the 5-FU continuous infusion.

Capecitabine (Xeloda) is a design drug that is absorbed unchanged from the gastrointestinal tract and after various enzymatic passages is converted into 5-FU in the tissues. In the liver, Xeloda is converted firstly into 5 ϕ -deoxy-5-fluorocytidine (under the action of carboxylesterase), and then into 5 ϕ -deoxy-5-fluorouridine (by histadine deaminase). It is finally converted into 5-FU by thymidine phosphorylase (TP). This latter stage is particularly important in the site of the tumour where the presence of TP is greater than in the liver or the rest of the tissues. Capecitabine has been developed without modulation by LV and in pivotal studies (European and USA) it has shown the same results in terms of survival and time to progression as those of the Mayo Clinic schedule, with response rates being even higher (26.6% vs 17.9%, $p=0.013$) (Van Cutsem 2001 and

Hoff 2001). In a pooled analysis of both studies (Cassidy 2002) performed on a total of 1207 patients randomized to receive Capecitabine (1250 mg/m² twice daily on days 1-14 every 21 days) or the Mayo Clinic 5-FU/LV regimen, Capecitabine proved to be safer with a lower incidence of diarrhea, stomatitis, nausea, alopecia and neutropenia and a lower rate of neutropenic fever and hospitalization requirements. Importantly, it should be highlighted that most of the patients (66%) in this study did not require a dose reduction of Capecitabine.

CAPECITABINE + OXALIPLATIN:

Oxaliplatin is a third-generation platinum having synergistic activity with 5-FU, which shows activity in first- and second-line colorectal cancer (Díaz-Rubio 1998, Machover 1996) and in combination with 5-FU/LV it has been shown to be superior to 5-FU/LV alone in two randomized studies (De Gramont 2000, Giacchetti 2000) in terms of response and time to progression. A phase I study (Díaz-Rubio 2002) of Capecitabine in combination with Oxaliplatin (XELOX) conducted on 23 patients led to recommend the following doses for phase II studies: Capecitabine 1000 mg/m² twice daily on days 1 and 14 followed by one week' treatment-free rest period, and Oxaliplatin 130 mg/m² as a three-weekly schedule. Dose-limiting toxicity was diarrhea (17% grade III). In this study, the efficacy in colorectal cancer in terms of partial response reached 55%, which is highly interesting considering that these patients had previously received other chemotherapy regimens. More recently these preliminary results have been confirmed by a phase II study (Sastre 2002). This study called XELOX was conducted on a total of 96 patients with advanced colorectal cancer and it showed a 55% partial response and 32% stable disease rate, with a median duration of response of 8.9 months. One-year survival was 67% and mean survival was 19.5 months. On the other hand, XELOX combination proved to be safe. The most relevant grade III/IV toxicities were diarrhea (14%), nausea/vomiting (11%), neutropenia (8%), thrombocytopenia (5%). Peripheral neuropathy related to Oxaliplatin occurred in 11% and grade III hand-foot syndrome in 2% patients.

Other study (Borner 2002) conducted by the Swiss group SAKK used a rather similar schedule except that Capecitabine doses were similar to those recommended in monotherapy (1250 mg/m² twice daily). Thirty-four patients were treated in first line showing a response rate of 44% and 23 patients were treated in second line with a response rate of 22%. Diarrhea was more frequent, therefore the use of a higher dose does not

add to efficacy. In spite of the fact that the two week's Capecitabine treatment followed by one week' treatment-free rest period schedule is being consolidating, there are also other possibilities. A randomized phase II study from Austria (Scheitauer 2002) is comparing the above-mentioned schedule (XELOX) to other schedule aimed to investigate dose-intensification of Capecitabine. In the latter situation, Capecitabine is being given at 3500 mg/m² (total dose) on days 1-7 and days 14-21 every 4 weeks, plus oxaliplatin (XELOX2). Toxicity found was similar and in the test arm with dose-intensification more responses (54% vs 42%) and an improved time to progression (10.5 vs. 6 months) have been observed. There are no survival data available at the moment.

At the present time, the Spanish group TTD is conducting a phase III study to compare XELOX combination (Capecitabine: 1000 mg/m² twice daily on days 1-14 every three weeks and Oxaliplatin: 130 mg/m² every 3 weeks) versus 5-FU given as continuous infusion (TTD-type) plus Oxaliplatin. This study would allow elucidating if Capecitabine may replace 5-FU continuous infusion with the added benefit of being more convenient for patients.

CAPECITABINE + CPT-11:

In parallel to these studies investigating Capecitabine and Oxaliplatin combination, a number of studies have been initiated to test Capecitabine in combination with CPT-11. It is well known that CPT-11 and 5-FU/LV combinations, given either as bolus or continuous infusion (Douillard 2000, Saltz 2000) have been shown to be superior to FU/LV as monotherapy in terms of response, time to progression and overall survival. The rationale for the combination of Irinotecan and Capecitabine lies in the additive effects that have been shown on the basis that CPT-11 seems to enhance the activity of thymidine phosphorylase and also in the different toxicity profiles of both drugs. These studies have been aimed to identify the regimen recommended for phase II and III trials that are ongoing at present.

The German phase I-II study (Schleucher 2001) recommends a two weeks' Capecitabine treatment (1000 mg/m² twice daily on days 1-14) followed by one week' treatment-free rest period schedule, and CPT-11 at the dose of 70 mg/m²/wk. Dose-limiting toxicities were diarrhea and neutropenia with a 42% activity in terms of response rate.

On the contrary, the French trial (Delord 2002) investigated 23 patients, 5 dose levels, and finally recommended the two-weekly capecitabine schedule (1000 mg/m² twice daily) plus CPT-11 250 mg/m² every three weeks. In 16 evaluable

patients there was one partial response and 13 showed stable disease. Similar conclusions can be drawn from the joint phase I-II study from United Kingdom and Netherlands (Kerr 2001) that recommends the same schedule. In this latter investigation the response rate seen in the 27 patients assessed so far was 48%, with a 41% stable disease rate.

Finally, a phase II Italian study (Bayeta 2001) investigated two different schedules of Xeloda plus Irinotecan. In both arms, capecitabine was given at 1250 mg/m² every 12 hours for two weeks, and CPT-11 was given either at 300 mg/m² on day 1 every three weeks or at 150 mg on days 1 and 8 every three weeks. The final dose recommended is 1000 mg/m² for Xeloda and 240 mg/m² for CPT-11 every three weeks. Response rate was 33% and the incidence of grade III/IV diarrhea was 32%.

These studies suggest that the dose recommended for phase II and III studies is as follows: Xeloda 1000 mg/m² every 12 hours on days 1-14 every 3 weeks, and CPT-11 250 mg/m² every three weeks. This schedule is being explored in phase III studies. The EORTC has designed a phase III study to compare this combination schedule versus 5-FU/LV (as continuous infusion) plus irinotecan (Douillard schedule). Regarding QUASAR 2 study, patients are randomized to receive FU/FA for 6 months (Mayo Clinic or Roswell Park schedules) versus capecitabine plus irinotecan (both given at the doses stated above). Furthermore, this study has a particular feature as it includes analyses of both polymorphism and TS and DPD expression.

In summary, it can be concluded that Capecitabine in combination with either Oxaliplatin or Irinotecan can be a good alternative to those regimens containing 5-FU. These two combinations offer excellent prospects in terms of response and tolerability rates, but there is no evidence so far for differences between Irinotecan and Oxaliplatin. Recently the preliminary results of a randomized phase II study comparing Capecitabine plus irinotecan versus Capecitabine plus oxaliplatin (Grothey 2002) have been reported. In both cases, capecitabine was given at 1000 mg/m² twice daily on days 1-14 every three weeks, oxaliplatin at 70 mg/m² on days 1 and 8, and irinotecan at 80-100 mg/m² on days 1 and 8. Grade III/IV toxicities for diarrhea were similar (11% vs. 13%). Response rates have been reported to be of 43% and 37% and those for stable disease of 41% and 37%, respectively. There was no difference in terms of time to progression or survival. Obviously it will be necessary to await for the phase III trials to draw the final conclusions of these combinations that seems active and more safe and comfortable for the patient.

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NOTAS:

Raltitrexed in combination with other drugs in the treatment of advanced colorectal cancer

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Raltitrexed ("Tomudex" – TOM) is a possible and convenient alternative to 5-fluorouracil (5FU) in the treatment of advanced colorectal cancer (ACC): this agent has a peculiar mechanism of action and a toxicity profile which is distinct from 5FU and also from the innovative compounds irinotecan (CPT-11) and oxaliplatin (OHP). Therefore, a combination between TOM and these drugs is warranted and the results are expected to be positive.

TOM + 5FU

Based on preclinical observations (indicating a sequence-specific additive or synergistic cytotoxicity), a number of phase I and II trials combining TOM and 5FU (bolus, infusion or oral analogues) have been performed in first- or second-line therapy. Generally, the 2 drugs can be combined at nearly full doses and satisfactory response rates (from 14 to 50%) with an acceptable toxicity have been reported (1). Subsequently triple combinations including these two compounds have been designed, with promising results (2).

TOM + OHP

Also for this association, in vitro and phase I studies have pointed out an additive effect for the two agents (3,4). The recommended dose is: TOM 3 mg/ sqm and OHP 130 mg/ sqm (both every 3 weeks), with fatigue and nausea/vomiting as the dose-limiting toxicities. The response rates are about 50% and are comparable to those achieved with OHP and 5FU/LV combinations (5, 6, 7). Also the median survival (about 15 months) seems to be similar. A satisfactory activity was reported also for patients pretreated with a fluoropyrimidine/LV-based chemotherapy (8).

TOM + CPT-11

In vitro studies have demonstrated synergistic activity with a short-term exposure to SN38 (the active metabolite of CPT-11) followed by TOM (9), whereas the reverse sequence has an antagonistic effect. Based on previous phase I trials (10), phase II studies have been launched and an activity of 40-50% has been observed, even though a substantial toxicity has been detected (11).

TRIPLE COMBINATIONS

It has been suggested that the combination of TOM, OHP and CPT-11 is able to obtain a high response rate (12), even though further studies are needed. In other experiences, TOM was combined with mitomycin C or UFT (1).

CONCLUSIONS

The combination of TOM with other active drugs is able to obtain significant response rates and an interesting survival. Phase III trials are urgently needed in this field.

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NOTAS:

The role of COX-2 inhibition in the treatment of colorectal cancer

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(CRC) is one of the most frequent cancers in the Western world. Despite advances in diagnosis and therapy, long-term survival has not improved over the last 4 decades, and nearly 50% of CRC patients will die of their disease. Early detection by screening of risk groups, surgical resections and adjuvant chemotherapy are the main available curative strategies. This presentation focuses on the potential role of cyclooxygenase-2 (COX-2) as target for treatment of micro-metastatic (adjuvant), and metastatic CRC.

Numerous epidemiologic studies have found that long-term users of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) have a 40-50% lower risk of colorectal adenomatous polyps and CRC than nonusers. Randomized clinical trials have confirmed that sulindac and the selective COX-2 inhibitor celecoxib (Celebrex[®]) effectively inhibit polyp growth and induce regression of polyps in patients with familial adenomatous polyposis (FAP). These data suggest that NSAIDs act on a very early state of carcinogenesis and may have a potential role in the chemoprevention of CRC.

COX-2 inhibitors may play a significant role in cancer treatment as well. Studies in rodents conclusively proved that non-selective and selective COX-2 inhibitors inhibit chemically induced colon carcinogenesis and induce tumor regressions in colon xenografts. In these animal models, celecoxib induces a dose dependent inhibition during early and late stages of tumor formation. In mouse models that resemble human FAP, and the Lewis lung carcinoma model, tumor formation was inhibited by selective genetic inactivation of COX-2 or by treatment with selective COX-2 inhibitors.

Although the anti-carcinogenic mechanism of NSAIDs is not clearly understood, these data suggest that inhibition of the arachidonic acid metabolism via the COX enzymes, especially COX-2, is an important target. Substantial evidence indicates that the prostaglandin products (PGE₂ and PGI₂) of the COX-2 pathway are regulators of several hallmarks of cancer such as, stimulation of cell proliferation, inhibition of apoptosis, and stimulation of angiogenesis. In addition, several studies demonstrated a role for COX-2 in tumor invasiveness and immune suppression. These and other data indicate that COX-2 and COX-2 derived prostaglandins may play a major role in the development of cancer through numerous biochemical mechanisms. The role of COX-2 in cancer promotion and progression is supported by the clinical findings that COX-2

expression is often increased in various human cancers, including colon cancer, and that high COX-2 expression is often related to advanced tumor stage and poor prognosis. COX-2 is undetectable in normal colon epithelium but is detectable in 40% of adenomatous polyps and in more than 80% of CRCs.

In light of these data, clinical trials designed to assess the use of selective COX-2 inhibitors in the therapy of human CRC (and other COX-2 expressing cancers) seems justified.

CLINICAL RESEARCH OF COX-2 INHIBITORS IN CRC

The outcome of patients with stage II and III CRC will be investigated in 2 phase III trials evaluating COX-2 inhibitors as adjuvant therapy: the Pan-European Trials in Adjuvant Colon Cancer (PETACC)-5 ACTION trial (Adjuvant Celecoxib Therapy in Oncology); and the Cancer Research Campaign VICTOR trial (VIOXX in Colorectal cancer Therapy: definition of Optimal Regimen).

In the VICTOR trial (stage II and III CRC) rofecoxib (Vioxx[®]) will be given during 2 and 5 years following completion of adjuvant chemotherapy.

In the ACTION trial (stage III CRC) celecoxib will be administered simultaneously with chemotherapy and during 3 years of follow up. The ACTION trial will assess the interaction of adjuvant chemotherapy and COX-2 inhibition during simultaneous administration, which may contribute to an anti-tumor effect in micrometastatic disease.

It has been demonstrated that several anticancer modalities, including radiation and cytotoxic chemotherapy, kill tumor cells via induction of apoptosis. Because COX-2 is a factor that contribute to apoptosis resistance in cancer cells, COX-2 inhibitors may enhance the effect of chemotherapeutic agents or radiation. Several pre-clinical studies have reported that selective inhibition of COX-2 simultaneous with radiation results in an enhancement of the radiotherapy effect on malignant tissue without increase of radiation damage of normal tissues. Celecoxib has shown to enhance the anti-tumor activity of CPT-11 and 5-FU in animal models and to ameliorate the severity of irinotecan-induced diarrhea.

Randomized phase III studies are planned in patients with metastatic CRC. For example, a randomized phase III study is being planned to evaluate the potential for increased efficacy and reduced toxicity when celecoxib is combined with an irinotecan-based regimen.

Role of extended lymphadenectomy in gastric cancer

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SUMMARY

Patients with gastric cancer have a poor prognosis. Surgery is the only treatment modality offering hope for cure. However, even after curative surgery, the five-year survival rate is still about 30%. Even though the incidence of early gastric cancer is up to 40% of all cases (surgically curable) in Japan, in Western countries most of the patients are diagnosed at an advanced stage, when curative surgery is no longer possible. Most patients die of locoregional recurrence or distant metastasis. Therefore, every attempt should be made to increase early diagnosis and to find additional prognostic factors which can be determined preoperatively. Operations with extended lymphadenectomy are associated with higher morbidity and mortality rates, while a possible survival benefit is not proven in Western countries. The five-year survival results of two large prospectively randomized, controlled trials (The Dutch Gastric Cancer Trials and the British Medical Research Council Trial) comparing limited lymphadenectomy (D1) to extended lymphadenectomy (D2) are still being awaited. In light of increased morbidity and mortality rates associated with extended lymphadenectomy, the limits of surgical possibilities for the treatment of gastric cancer seem to be reached. Adjuvant radiotherapy and chemotherapy are demonstrated to not give an additional survival advantage compared to surgery only. Development of more active combination chemotherapy regimens and results in locally advanced gastric cancer are encouraging. Therefore, to evaluate the place of preoperative chemotherapy in potentially operable gastric cancer, two randomized trials have been initiated in the Netherlands and Great Britain. Gastric cancer should be considered a malignancy which requires a multidisciplinary approach of a specialized team consisting of committed specialists. New treatment modalities should only be applied to patients in clinical trial settings with dedicated clinicians.

INTRODUCTION

Because of its poor prognosis and for being the most frequent cause of cancer-related deaths worldwide, gastric cancer used to be called the captain of death. Even though its mortality rate has gradually decreased, this decrease is mostly attributable to its worldwide declining incidence. However, gastric cancer is still the second most common cause of cancer-

related deaths in the world.¹ Surgery remains the cornerstone of treatment for gastric cancer, but little of the surgical approach has stayed the same since Japanese investigators started reporting better survival rates for all stages. They have ascribed their superior survival rates to early detection and extensive lymphadenectomy.^{2,3} In Japan, so-called early gastric cancer (tumour confined to mucosal or submucosal layer) is found in up to 40% of patients and a D2 resection is employed as standard surgical procedure, while in the Western countries generally a limited lymphadenectomy (D1) is employed. The Japanese have argued that the D2 resection should be performed in all patients with invasive gastric carcinoma, including those with early gastric cancer and that a D3 lymphadenectomy should be performed in all patients with advanced gastric cancer with serosal invasion.^{4,5} However, the Japanese results are based on retrospectively collected data only. Therefore, improved results of surgical treatment of gastric cancer in Japan could not only be attributed to extensive lymph node dissection, but also to the fact that early gastric cancer and other more favorable prognostic factors are much more common. Besides, in most Western countries lymph nodes are regarded as indicators rather than governors of disease.⁶ According to this theory, extended lymph node dissection merely improves the accuracy of tumour staging and thus induces a so-called stage migration by which a better stage specific survival will be achieved, while the overall survival is not altered. If we want to develop and apply new diagnostic and therapeutic approaches for a disease this common, with such a poor prognosis, we have to treat our patients in (good quality) controlled randomized multicenter clinical trials before introducing new approaches in daily practice.

STAGING

To end the confusion caused by different definitions of the R-classification in Japanese and UICC nomenclature, in September 1993 it was recommended (at the meeting of World Health Organization Collaborative Cancer Group) to use 'D'-classification to indicate the extent of lymph node dissection and the 'R'-classification to indicate the residual tumour-situation after resection.⁷ According to the rules of the Japanese Research Society for Gastric Cancer (JRS GC), the stomach is divided into three sectors: upper third or C, middle third or M and lower third or A. The exact nodal groups, which require removal for potentially curative resection depend on the location of the primary tumour. A D1 resection removes all N1-level (along the splenic and left gastric artery and coeliac axis) nodes and a D3 resection removes N1, N2 and N3-level

(hepatoduodenal and root of the mesentery) nodes.⁸ In the R-classification, R0 means no residual tumour (macroscopical and microscopical no residual tumour), whereas R1 means microscopical residual tumour and R2 means macroscopical residual tumour.

In order to find an explanation for the discrepancy in survival rates between Japan and Western countries, patient data from Japan, Germany and the Netherlands were compared. This study showed that imbalances in prognostic factors and staging systems could not explain satisfactorily the differences in 5-year survival rates, suggesting that the better outcome in Japanese patients could be treatment-related.⁹

RANDOMIZED TRIALS ON EXTENT OF LYMPHADENECTOMY

To analyze the role of extended lymphadenectomy and extent of gastrectomy (total versus subtotal) for gastric cancer treatment, several prospectively randomized trials were undertaken in Western countries. The first randomized trial dealing with the issue concerning the place of extended lymph node dissection (D2) in the treatment of gastric cancer by Dent et al. (South Africa)¹⁰ was warning against extended lymph node dissection. D2 resection was associated with a greater blood transfusion requirement increased morbidity and a longer hospital stay, while there was no survival advantage. The fact that 403 patients were randomized in this trial and that only 43 patients (11%) were eligible, made the interpretation of these results very difficult. More than 6 years later, the second warning came from Hong Kong.¹¹ In this trial, comparing D1 subtotal gastrectomy with D3 total gastrectomy in patients with antral carcinoma, increased morbidity (intra-abdominal sepsis) associated with extended dissection was demonstrated again. Although the patients in the D1 group had a significantly better survival than the patients in the D3-group, a straight forward interpretation of this finding is not possible. Because, not only the number of the analyzed patients was small, but also subtotal gastrectomy combined with limited lymphadenectomy (D1) was compared with total gastrectomy combined with extended lymphadenectomy (D3), while the extent of lymphadenectomy, as well as the place of total and subtotal gastrectomy are still debated in gastric cancer surgery. In a prospective controlled study comparing total and subtotal gastrectomy for antral carcinoma by Gouzi et al (France)¹² no difference in postoperative mortality and survival rate was found. But in another study by Bozzetti et al. (Italy)¹³, in interim-analysis an increased morbidity and mortality was found in patients undergoing total gastrectomy, while survival results are still to be awaited.

Two other prospectively randomized trials, one in the Netherlands by the Dutch Gastric Cancer Group (DGCG) and

the other in Great Britain by the Medical Research Council (MRC) comparing D1 with D2 dissection were completed in 1993. In the DGCG trial 1078 patients were entered, 711 of these patients underwent a curative resection in intent. In the British MRC trial 400 patients were included. Strict quality control measures were taken in the DGCG Trial to guarantee the intended difference between these two resection types. 14 'Contamination' (dissection of lymph nodes outside the indicated area) and 'non-compliance' (incomplete lymph node dissection) were defined and acknowledged as possible confounders of the outcome. Also a beneficial effect of extended lymph node dissection by stage migration was assessed in this trial.¹⁵ Both these trials with a large number of patients demonstrated that extended lymphadenectomy is associated with significantly higher morbidity and mortality rates compared with limited lymphadenectomy.^{14,16}

Despite numerous retrospective comparisons of limited and extended lymphadenectomy, of which the German multicentre observation study¹⁷ is the most important one, in which a survival advantage was found in patients undergoing extended lymphadenectomy for gastric cancer, a beneficial effect on survival remains to be demonstrated in prospectively randomized trials. Although these kind of studies are very important, their applicability in general practice is not possible, because of a case selection bias due to the nature of every retrospective analysis. In a meta-analysis of randomized trials studying the effect of adjuvant chemotherapy after a curative resection, only a marginal survival advantage was found.¹⁸

HOW CAN WE DECREASE MORBIDITY / MORTALITY OF THE PROCEDURE

Randomized trials with a large number of patients demonstrated that extended lymphadenectomy (D2 and D3) is associated with significantly more morbidity and mortality compared to the D1 resection. Even though a selection bias (inclusion criteria) is inevitable in trials, these multicenter trials do give a good reflection of the present situation, because they are the closest to the real situation. Five-year survival rates were similar in the two groups: 45 percent for the D1 group and 47 percent for the D2 group (95 percent confidence interval for the difference, -9.6 percent to +5.6 percent). The patients who had R0resection (i.e., who had no microscopical evidence of remaining disease), excluding those who died postoperatively had cumulative risks of relapse at five years of 43 percent with D1 dissection and 37 percent with D2 dissection (95 percent confidence interval for the difference, -2.4 percent to +14.4 percent). Patients with lymph node metastases limited to the first echelon (N1), generally with stage II and III A disease, may benefit from D2 dissection. Another aspect which is still not

clear is who should perform these operations?¹⁹ However, it is very likely, that gastric cancer is treated best by a multidisciplinary team with a committed surgeon, pathologist, radiologist and medical-oncologist. Perioperative care deserves more attention as well, because also in Japan, where gastric cancer surgery is performed by gastric cancer surgeons only, extended lymphadenectomy is associated with as high morbidity rates as in the West, but without increased mortality. These facts can not be full explained by patient- or tumour-related factors, such as age, weight, height/weight index and concomitant disease.^{9,20} In order to minimize complications associated with pancreatic tail resection and splenectomy, the Japanese have developed pancreas and spleen preserving techniques. The results achieved with these methods justify a more refined surgical approach: pancreatectomy and splenectomy 'de necessité' should be applied instead of 'de principe'.^{21,22}

MULTIMODALITY TREATMENT

Preoperative (neoadjuvant) systemic chemotherapy seems a promising approach. By giving systemic treatment, both the primary tumour as well as distant (micro) metastases can be handled, which may lead to downstaging. Therefore, it is expected that more patients can have resections, either for cure or for palliation, leading to an improvement of the survival rates and quality of life. The value of preoperative FAMTX in operable gastric cancer was investigated in the Netherlands in a prospective randomized trial of which the end results will be presented. Currently a joint study with ECF with the MRC is ongoing. Trials are the only way for developing future standardized treatments without exposing our patients to improven and thus potentially dangerous treatment fads.

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Localized Gastric Cancer: Postoperative and Preoperative approaches

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Patients with localized gastric carcinoma need careful and complete attention as some are likely to be cured when an appropriate management is offered. The outcome also depends on T-stage, N-stage, and type of resection accomplished (R0, R1, or R2). In addition, proximal location has an adverse outcome for these patients. Although, molecular markers could emerge as indicators of outcome, none is practical at present. Expression of PDGF- α , Her-2/neu, TGF- β , and EGFR has been associated with inferior survival. Also, high TS and ERCC1 expression has been linked to poor prognosis among patient receiving fluoropyrimidine and platinum based chemotherapy. Overall, patients with local-regional gastric carcinoma remain at high risk for systemic and local-regional relapse.

The patterns of care analyses by the American College of Surgeons and American Cancer Society suggest that the 5-year survival rates for patients with resected stage II, IIIa, IIIb, and IV gastric cancer are 34%, 20%, 8%, and 7%. These are dismal statistics. Numerous clinical trials of adjuvant systemic chemotherapy have consistently failed to improve the outcome of these patients. Thus chemotherapy alone as postoperative adjuvant is not a consideration in the West. However, combined modality approach of chemoradiotherapy has resulted in significant survival advantage in time-to-progression and overall survival.

On the basis of the activity of chemoradiotherapy in patients with unresectable or residual local disease, investigators have studied postoperative adjuvant chemoradiotherapy. Both single-arm and randomized studies have been conducted, and results have shown that concurrent chemotherapy and irradiation is feasible. However, early chemoradiotherapy trials suffered from inadequate number of patients, heterogeneous treatment groups, poor randomization schemes, high dropout rates, and lack of proper control groups.

The Gastrointestinal Cancer Intergroup 0116 trial randomly assigned 603 patients with stage Ib-IV (M0) gastric cancer who have undergone curative resection to surgery alone or surgery followed by 5-FU, folinic acid, and external-beam irradiation (Figure 1). With a median followup of 5-years, 3-year overall survival rate (50% versus 41%; P = 0.005) and the 3-year

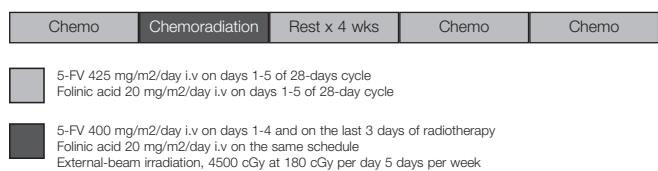
disease-free survival rate (48% versus 31%; P = 0.001) were both better in the treated group. This trial also shows that extensive lymphadenectomy is not commonly performed in the United States. Only 10% of patients entering the trial had D2 dissection; 36% had D1 dissection. Most patients (54%) had less than a D1 dissection. Given the large number of patients and the inclusion of a surgery alone control group, postoperative chemotherapy plus chemoradiotherapy should now be considered the standard of care for patients who have undergone curative resection. The European investigators now have an opportunity to ask the question if chemoradiotherapy can improve the outcome of patients undergoing D1+ surgery.

PREOPERATIVE CHEMORADIO THERAPY

The strategy of preoperative chemoradiotherapy is also under investigation. In a pilot study, 24 patients were treated with 45 Gy of external beam radiation at 1.8 Gy per day 5 days per week concurrent with continuous infusion 5FU 300 mg/m²/day on days of radiation. Surgery was carried out 4 to 6 weeks after completion of chemoradiotherapy in 19 (83%) of patients. Intraoperative radiotherapy (10Gy) was given at resection. Complete pathologic response was observed in 2 (11%) of patients and major treatment effect was observed in 63 patients. Two additional trials in 80 patients also show consistency in the path CR and feasibility of induction chemotherapy before chemoradiotherapy.

These trials indicate that preoperative chemotherapy is feasible and that delayed definitive local therapy (surgical resection) can be carried out without adverse impact on rate of R0 resections. Larger randomized trials with prospectively defined endpoints will be needed.

Treatment scheme for INT 0116.



El tratamiento del cáncer gástrico avanzado de 5-FU a ECF. La experiencia del grupo TTD.

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El tratamiento del cáncer gástrico avanzado ha sufrido pocos cambios esenciales en los últimos diez años. Aunque se trata de una neoplasia como quimiosensible, y de hecho las tasas de respuestas objetivas de varias combinaciones se aproximan al 50%, la mediana de supervivencia no supera los 8-10 meses y la proporción de supervivientes a los dos años no supera el diez por ciento. Sin embargo, la investigación clínica, promovida principalmente por instituciones académicas y grupos cooperativos, ha permitido destacar en varios estudios randomizados que la quimioterapia es un tratamiento eficaz para mejorar los síntomas y la calidad de vida de los pacientes tratados, y además prolonga significativamente la supervivencia cuando se compara a una opción de sólo cuidados de soporte. Por otra parte, la instauración temprana del tratamiento en pacientes asintomáticos retrasa la aparición de síntomas derivados de la progresión tumoral y mejora la expectativa de supervivencia. Por ello está bien establecido que la quimioterapia es un instrumento útil en el tratamiento de pacientes con cáncer de estómago avanzado. Sin embargo, el esquema terapéutico más eficaz o tratamiento estándar dista de estar bien definido.

La experiencia del grupo TTD en estudios clínicos de cáncer gástrico avanzado se remonta a las actividades iniciales del grupo en la década de los ochenta. En aquellos momentos parecía claro que esquemas de poliquimioterapia conocidos como de segunda generación podían ser superiores a otros esquemas más convencionales. El primer estudio randomizado del grupo TTD en este contexto nos ayudó a comprender que la población tratada es distinta a la de otras enfermedades, ya que se trata en general de pacientes debilitados, probablemente malnutridos por la gastrectomía previa, con un elevado volumen tumoral y, por ello, con un estado general mal conservado. Un tratamiento experimental más intensivo, estudiado por un centro académico en una serie seleccionada de pacientes, (EEP) era capaz de inducir una mayor tasa de respuestas objetivas que un tratamiento clásico mejor tolerado (FEM) (30% versus 13%). Sin embargo, inducía una probabilidad de supervivencia mediana más baja (7,9 versus 4,2 meses), debido al deterioro del performance status relacionado con una elevada toxicidad hematológica y

gastrointestinal. Otros estudios randomizados internacionales llegaron a conclusiones similares y los esquemas similares a EEP-EAP fueron abandonados.

El desarrollo de nuevos esquemas de quimioterapia en el cáncer gástrico avanzado fue de algún modo paralelo con los avances en el tratamiento del cáncer colorectal. Otros esquemas de tercera generación se basaban en el uso de modulación bioquímica de 5FU por ácido folínico o metotrexate con la adición de antraciclinas y/o cisplatino. Así el esquema FLEP, estudiado por nuestro grupo en un diseño de fase II, obtenía una tasa de respuestas del 35% con una supervivencia mediana de ocho meses. Posteriormente, en un ensayo randomizado fase III el esquema FLEP fue significativamente superior a FAMTX sólo en la tasa de respuestas objetivas (22% versus 9%); mientras que las diferencias en supervivencia no alcanzaron la significación estadística (7,2 versus 5,7 meses) en dicho ensayo. Esta observación relativa a fármacos o combinaciones con mayor eficacia, en cuanto a mayor reducción del volumen de enfermedad metastásica; pero que no pueden lograr efectos significativos en el incremento de la supervivencia es común en los resultados de la investigación terapéutica del cáncer gástrico avanzado, y su pone una barrera difícil de superar. Son escasos los estudios en los que un esquema de tratamiento implica un impacto cuantitativo de importancia clínica en este contexto.

El objetivo básico de tratamiento del cáncer gástrico avanzado es básicamente paliativo. Pretende controlar o retrasar la aparición de los síntomas de progresión tumoral con un mínimo coste de toxicidad, manteniendo un perfil favorable de efectos secundarios que se relacione con una mejora global en la calidad de vida de los pacientes. La mayoría de estudios de 5FU en cáncer de estómago eran en su forma de administración intravenosa rápida y escaseaban en los que la administración se basaba en la infusión continua. En un primer estudio fase II extendido a 89 pacientes con monoterapia, basada exclusivamente en la infusión continua semanal de altas dosis de 5FU (3 g/m²), este esquema mostró una tasa de actividad antitumoral del 18%, entre las que se apreciaron un 7% de respuestas completas y una probabilidad de supervivencia mediana de 6,9 meses. Posteriormente, otro ensayo fase II también extendido, en el que se incluyeron 149 pacientes, en el que al clásico esquema terapéutico del grupo TTD, se añadió una dosis de cisplatino (70 mg/m²), cada tres semanas. En este segundo estudio, la tasa de respuestas

Defining Targets for Advanced Gastric Carcinoma

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Advanced gastric carcinoma is a death sentence of the patient. This entity is diagnosed too frequently because of the lack of early detection programs in most of the world. Studies of molecular biology of gastric cancer have seriously lagged that of colon carcinoma. Molecular markers could emerge as indicators of outcome, none is practical at present. Expression of PDGF- α , Her-2/neu, TGF- β , and EGFR has been associated with inferior survival. All these and other markers can serve as targets. Much more work would be necessary to develop an effective strategy for the development of new targets. In addition to the development of new targets, one must consider changing the paradigm for treating patients with advanced gastric carcinoma. Currently, patients are treated with empiric chemotherapy until there is progression of cancer or intolerance to therapy but with the availability of new small molecules, it may be important to treat patients until maximum response followed by maintenance therapy using small molecules. In addition to molecular markers related to cell survival, growth, and metastases, the markers that are specifically connected to drug activity e.g., TS, DPD, TP, ERCC1 and others may prove useful in developing new strategies.

Another target is gastrin. Gastrin hormone receptors are frequently present on cancer cell originating from a variety of tumors including gastric carcinoma. Gastrin is represented in many forms. The polypeptide hormone, G17 gastrin, plays a major role in gastric acid secretion. It is also a known growth mediator of the normal gastric and small intestinal mucosa. This latter activity generated interest in G17 gastrin as a potential growth factor for tumors arising within the gastrointestinal (GI) mucosa. This was confirmed because gastrin peptides in preclinical setting increased the proliferation of GI cancer cell lines of human and animal origin both in vitro and in vivo.

Additional studies compared the mitogenic effects of gastrin on colorectal and gastric cancer cells obtained from subjects undergoing surgery. Sixty-nine percent of gastric cancer cells had an enhanced proliferation when exposed to G17 gastrin (greater than normal GI cells (1). Additionally, gastrin gene is activated in GI cancer cells but not in normal GI cells (2). This led to the observation of a G17 gastrin-mediated autocrine/paracrine growth pathway: malignant epithelial cells producing mitogenic gastrin peptides which can increase the proliferation of themselves and/or surrounding cells, thereby inducing a state of tumor autonomy (3,4).

One of the main gastrin species associated with tumor cells is C-terminal glycine-extended G17 gastrin (Gly-G17 gastrin). This peptide increases the proliferation of pancreatic, gastric, hepatic and colorectal tumor cell lines (4).

G17 gastrin, Gly-extended gastrin, G34 gastrin (a second gastrin species), and CCK have a common carboxyl terminus. It is known that this part of the molecule interacts with the CCKB/gastrin receptor (5). G17DT conjugate was developed in an attempt to generate antibodies against the amino-terminal end of G17 gastrin. G17DT conjugate is constructed from a synthetic 16-residue peptide comprising an epitope derived from the 9 amino-terminal amino acid residues of G17 gastrin and a C-terminal 7 amino acid residue spacer sequence terminating in a cysteinyl residue. The peptide is cross-linked via its C-terminal cysteine residue to a carrier protein, Diphtheria toxoid (DT), using the bifunctional cross-linker eMCS to form the G17DT conjugate. G17DT has been formulated in a water-in-oil emulsion suitable for intramuscular injection. Immunization with G17DT elicits antibodies that react specifically with G17 gastrin and Gly-G17 gastrin. The antibodies do not cross-react with any of the other hormones tested, including G34 gastrin and CCK. Antibodies elicited by G17DT inhibit the growth of human gastric and colorectal cancer cells, in both in vitro and in vivo animal models. G17DT did not cause any systemic side effects. No evidence was found for deleterious effects of long-term neutralization of G17 gastrin and Gly-G17 gastrin. The only significant side effect following immunization with G17DT is local reaction. A G17DT formulation has been developed that elicits a maximum immune response while exhibiting an acceptable local reactogenicity. Neutralization of the endocrine and autocrine/paracrine effects of G17 and Gly-extended G17 gastrin is proposed as the mechanism by which G17DT can reduce tumor growth and increase survival.

Antibodies raised in rabbits by G17DT immunization (Kd for G17 gastrin of 0.15 nM and for Gly-G17 gastrin of 0.47 nM) were administered intravenously to SCID mice injected intraperitoneally with MGLVA1 ascites cells (7.5×10^5 cells/animal). The effect of these antibodies on the survival of the animals was compared to that obtained with a combination treatment of 5-fluorouracil and leucovorin (both at 25 mg/kg., i.v.). Enhanced survival was similar to that achieved by treatment with 5-fluorouracil and leucovorin. Combination therapy with anti-G17 antibodies and 5-fluorouracil/Leucovorin led to an enhancement of survival compared to treatment with either G17DT or 5-fluorouracil/leucovorin ($p < 0.05$) alone. These results indicate that inhibition of G17 gastrin by two independent mechanisms reduced tumor growth with a resultant increase in survival.

Rectal cancer value of adjuvant treatment in relation to TME surgery

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ABSTRACT

One of the major problems in the treatment of rectal cancer has been the inability to achieve local control. The conventional surgical procedure, which involves blunt digital dissection, is associated with a high incidence of local recurrence.

In an attempt to improve local control and survival, many adjuvant treatment modalities have been investigated. In the context of conventional non-standardized surgical procedures, preoperative radiotherapy has shown to improve local control and overall survival.

In recent years treatment outcome has been extensively improved by the introduction of the TME technique as first described by Heald. This surgical technique resulted in such low recurrence rates and improved survival that the question had to be answered whether preoperative short-term radiotherapy is still beneficial in TME treated patients. This question was answered in the TME trial set up by the Dutch ColoRectal Cancer Group that randomised between standardized and quality controlled TME surgery alone and TME surgery preceded by short-term preoperative radiotherapy.

This paper reviews the developments in the treatment of resectable rectal cancer, highlights the results from the Dutch TME trial, and considers future directions in improving outcome.

LOCAL RECURRENCE: A MAJOR PROBLEM IN RECTAL CANCER

Local recurrence is a serious problem in the treatment of rectal cancer.[1] It causes severe disabling symptoms that are difficult to treat and often kill the patient. The basic conventional procedure that involves blunt dissection of the rectal fascia fails to remove all mesorectal tissue, which causes high recurrence rates from 15 up to 45%. [2] Additional radiotherapy has been given to in an attempt to improve local control after conventional surgery. Results of the studies that investigated the role of radiotherapy showed that preoperative radiotherapy is more effective than postoperative radiotherapy in reducing

local recurrence rates.[3] The Swedish Rectal Cancer Trial found that preoperative radiotherapy also improved the rate of survival at five years.[4] The results of a large meta-analysis[5] strengthened the idea that the combination of preoperative radiotherapy and surgery could improve overall and cancer specific survival compared with surgery alone.

The acknowledgement of the important role of circumferential margin involvement in the occurrence of local recurrences has led to the introduction of TME (Total Mesorectal Excision) surgery. The concept of TME was introduced by Heald at the North Hampshire Hospital in Basingstoke in 1979.[6] By using sharp dissection under direct vision a relative bloodless plane is followed along the outer surface of the rectum. This technique ensures a specimen with intact mesorectum with negative tumour margins in the majority of resectable (i.e. mobile) rectal cancers. Heald's first series of 122 curative anterior resections showed a cumulative risk of local recurrence at 5 years of 2.7% and overall corrected survival of 87.5% at 5 years.[7] These excellent results were matched in Enker's personal series of 246 curable Dukes' stage B and C patients of which only 18 developed a local recurrence. The actuarial cancer specific 5-year survival was 74.2%. [8] Aitken published a series of 64 patients that underwent a curative TME procedure: only one patient (1.6%) developed a local recurrence.[9]

Since the introduction of TME surgery has resulted in such low recurrence rates and improved survival, the question had to be answered whether adjuvant treatment is still capable of achieving any further improvement in outcome. As the skills and experience of the surgeon and the surgical technique are of major importance in achieving local control[10], standardization and quality control with respect to surgery is indispensable for evaluating the effects of adjuvant treatment.

THE DUTCH TME TRIAL

The Dutch Colorectal Cancer Group organised jointly with the Nordic Gastro Intestinal Tumour Adjuvant Therapy and the EORTC a large prospective randomised multicenter trial to investigate the efficacy of preoperative radiotherapy (5x5 Gy) in combination with standardized total mesorectal excision in patients with rectal cancer. Standardization and quality control of surgery, radiotherapy, and pathology were achieved by means of a monitoring committee of specially trained instructor surgeons, a panel of supervising pathologists and study coordinators for surgery, radiotherapy and pathology.

Eligibility criteria included histologically confirmed adenocarcinoma of the rectum without evidence of distant metastases. The inferior margin of the tumour had to be located not further than 15 centimetres from the anal verge and below the level of S1-2. Patients with fixed tumours were excluded as well as patients with locally treated (transanal resected) tumours.

Patients were enrolled between January 1996 and December 2000. A total of 1861 patients were randomly assigned to one of the two treatment groups. There were 1530 patients from 84 Dutch hospitals, 228 patients from 13 Swedish hospitals and 103 from 11 other European and Canadian centres. Of these 1861 patients, 56 were ineligible before randomisation, including 4 patients for whom there was no information on eligibility. Of the 1805 eligible patients, 1653 had a curative resection. Of the remaining 152 patients, 57 did not undergo a macroscopically complete resection, and of 95 patients distant metastases were discovered during the surgical procedure.

Before the start of the TME trial, there were doubts whether the excellent results obtained by specialized surgeons could be matched in a large multicenter trial. To investigate this, we compared the outcome in the Dutch TME trial patients that did not receive preoperative radiotherapy with the results from a former randomised trial, the Cancer Recurrence And Blood transfusion (CRAB) trial.[11] In this latter trial conventional, non-standardized surgery was performed. This analysis showed that introduction of TME had led to a substantial lower recurrence rate when only events within two years were analysed: 16.3% in the CRAB trial vs 8.6% in the TME trial. With this low recurrence rate in the TME trial, it was made clear that good local control can be achieved by general surgeons after a thorough surgical instruction. These results are in concordance with the report of Martling et al.[12] In this analysis a comparison was made between the Stockholm I and II randomised trials in which conventional surgery with or without radiotherapy was performed, and the TME project that introduced the concept of TME to surgeons in Stockholm: the 2-year local recurrence rates decreased from 14-15% to 6%.

The local recurrence analysis for all patients of the TME trial showed a 2-year local recurrence rate of 5.3%. In the TME group this rate was 8.2% and in the RT+TME group 2.4% ($p < 0.001$) (see figure 1). An effect of preoperative radiotherapy on overall survival could not be detected (see figure 2). The beneficial effect of preoperative radiotherapy was observed for all tumour locations 15 centimetres or less from the anal verge and for all TNM stages. In a univariate subgroup analysis however, this effect was not significant in patients who had lesions located more than 10 centimetres from the anal verge and in patients with TNM stage I and IV. Nevertheless,

multivariate tests indicated that the beneficial treatment effect did not differ among subgroups defined according to tumour location, TNM stage and treatment assignment. Therefore, the decision not to irradiate these patients should be made with reservation.

Based on experiences of former randomised trials[13], concerns have been expressed about the side effects of hypofractionated radiation. In this trial however, no other significant differences with respect to postoperative morbidity and mortality were found than an increase of perineal complications in the RT+TME group in patients that had an abdominal perineal resection.

PROCTOR-TRIAL

The successor of the Dutch TME-trial is the PROCTOR (Preoperative Radiotherapy and/Or adjuvant Chemotherapy combined with Tme-surgery in Operable Rectal Cancer) trial. So far, chemotherapy has shown to have little effect in combination with conventional surgery in the prevention of distant recurrences and improvement of survival. This may be partly explained by the high rate of local recurrence associated with conventional procedures that might have masked the beneficial effect of chemotherapy. The additional value of postoperative chemotherapy (5-FU/Leucovorin according to Mayo or Nordic regime) is now investigated in patients with stage II and III rectal cancer that had a R0-resection. The main objective is to examine whether postoperative chemotherapy leads to a substantial improvement in overall survival. The overall survival in the arm treated without chemotherapy is to be expected 60%. Assuming that postoperative chemotherapy leads to an improvement in overall survival from 60 to 70%, 500 patients are needed per arm. The secondary objective is to investigate the effect of chemotherapy on local and distant tumour control. This trial is open to accrual.

DISCUSSION

In recent decades, substantial progress has been made in the treatment of rectal cancer. New surgical techniques have played a major role in improving treatment outcome. Local control and survival have been improved by the TME technique. TME is accomplished by precise sharp dissection within the true pelvis around the integral mesentery under direct vision, enveloping the entire midrectum. Apart from the beneficial effect on local recurrence and survival, the TME dissection is also associated with a higher incidence of sphincter preservation and of pelvic and autonomic nerve preservation. This implies avoiding both colostomy and

impotence, thus increasing patient's quality of life. One side effect of the higher rate of sphincter saving procedures is however the increased risk of anastomotic leakage.

To improve results of surgery many adjuvant treatment regimes have been tested. The studies published so far however, have been carried out without a clear definition of the surgical procedure to be followed and without sufficient quality control. In none of the trials criteria were formulated and controlled with respect to safety margins, excision of the mesorectum and lymph node dissection. Currently, global local recurrence rates of less than 10% can be achieved with standardized TME surgery alone. The question therefore to be answered is whether a further improvement can be obtained by adjuvant therapy.

In this paper an overview was given on the efforts that have been made to reduce the local recurrence risk in patients with rectal cancer. Due to severe and disabling symptoms caused by local failure, local pelvic control is generally accepted as a main objective of any adjuvant treatment. The Dutch TME trial clearly showed that short term preoperative radiotherapy could reduce the risk of local recurrence more than 3-fold in the setting of standardized TME surgery (8.2 vs 2.4% after a median follow-up of 2 years, $p < 0.001$). In terms of tumour biology, preoperative radiotherapy is to be preferred to postoperative irradiation as tumour cells before surgery have higher oxygen saturation and are therefore more sensitive to irradiation. Furthermore, preoperative radiotherapy devitalises tumour cells that maybe dispersed during the operation, and reduces therefore the risk of metastasis. On the other hand, postoperative radiotherapy allows exclusion of patients with rectal cancer stages Dukes' A and D. To guarantee its effectiveness postoperative irradiation should start not later than 4 to 6 weeks after surgery to prevent tumour cell proliferation in the postoperative, fibrous and hypoxic tissues. However, many patients turn out not to be fully recovered from the operation at this point in time, which causes a delay in receiving the adjuvant radiotherapy. This lack of compliance jeopardises therefore the possible benefits of postoperative radiotherapy.

The Dutch TME trial is one of the first trials that evaluated the role of adjuvant treatment in combination with TME surgery. Standardization of surgery, radiotherapy and pathology was achieved. The accrual went fast and the trial showed to be feasible. It was clearly shown that short-term preoperative radiotherapy has a beneficial effect in TME treated patients.[14] Many aspects of this trial have been strictly quality controlled. There are extensive data on quality of life as well as a tumour bank of fresh frozen material with a high potential for future micro array analyses. This will enable the development of tailor made treatment modalities in the future.

During the last ten years, it has become clear that adjuvant treatment has the potential of decreasing local recurrence risk and improving overall survival. Total mesorectal excision has become the new standard of operative management of rectal cancer. To identify preoperatively patients that will benefit most likely from (neo-)adjuvant therapy, emphasis needs to be put on better preoperative staging and imaging. Therefore, diagnostics and surgical treatment must be standardized in current and future trials to assess the value of adjuvant therapy in a reliable way.

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Ponencias

Simposio S atelite

Registro GEIS. Análisis de pacientes con GIST. Proyecto GIST

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INTRODUCCIÓN

El Grupo Español de Investigación en Sarcomas (GEIS) inició su andadura en Junio/94 con el diseño y ejecución de diversos ensayos clínicos en pacientes afectados de sarcomas somáticos y viscerales. Una de las vías de investigación que se empezaron a desarrollar fue la epidemiológica, haciendo posible el Registro GEIS. Este registro no tiene base poblacional sino hospitalaria, y ha ido incorporando pacientes diagnosticados de sarcomas en nuestros hospitales. En estos momentos hay más de 1.100 pacientes registrados sin contar con datos del 2001 y del 2002. Está prevista una actualización en Febrero/03 en la que esperamos llegar a más de 3.000 casos. En la actualidad el grupo lo constituyen 50 hospitales distribuidos por todo el territorio nacional.

Análisis de factores pronósticos en GIST:

Se han revisado 69 pacientes con GIST registrados en nuestra base de datos en un periodo entre 1994 y 1999. Las variables analizadas incluyeron edad, sexo, tiempo entre el primer síntoma y el diagnóstico, tamaño del tumor primario, número de mitosis y la presencia de metástasis.

Hubo 24/69 pacientes en el momento del diagnóstico, las dos localizaciones más frecuentes fueron hígado (13/24) y localización intra-abdominal (12/24).

El análisis estratificado de supervivencia por factores pronósticos se evaluó mediante el método de Kaplan-Meier. El modelo de riesgo proporcional de Cox se usó para el análisis uni y multivariante.

RESULTADOS

La edad (≤ 50 or >50 a), Diámetro máximo del tumor primario (≤ 9 cm or >9 cm) y presencia de metástasis fueron factores pronósticos en el análisis univariante, permaneciendo la edad y las metástasis como factores pronósticos independientes en el análisis multivariante.

PROYECTO ACTUAL

SUPERVIVENCIA									
	n	muert.	3 m	6 m	12 m	3 a	5 a	8 a	DI*
GIST	69	21	94,2	91,0	89,2	57,4	53,6	42,1	9,78

*DI (muertes x meses⁻¹ x 1000)

GIST	n	muertos	Tiempo a riesgo	DI	RR	IC95%
Edad						
≤50	13	2	961,57	2,08		
> 50	56	19	1184,30	16,05	7,7	1,8-33,1
Sexo						
Mujer	33	9	1301,07	6,92		
Varón	36	12	844,80	14,20	2,1	0,9-4,9
Tiemp. a Dco.						
≤ 3 mes	42	11	1373,47	8,07		
> 3 mes	27	10	772,41	12,95	1,6	0,7-3,8
Tamaño						
≤ 9 cm	35	7	1420,90	4,93		
> 9 cm	34	14	724,97	19,31	3,9	1,6-9,7
Mitosis						
≤ 9	31	11	840,83	1,31		
> 9	19	5	354,81	1,41	1,1	0,4-3,1
Ganglios						
No	59	18	1905,67	9,45		
Sí	9	3	193,53	15,50	1,6	0,5-5,6
Metástasis						
No	45	9	1856,97	4,85		
Sí	24	12	288,90	41,54	8,6	3,6-20,3

Análisis univariante. Distribución por variables.

	3m	6m	12m	3a	5a	IC95%	p
Edad							
≤50	100	100	100	88,9	88,9		
> 50	92,9	88,9	86,8	45,3	36,2	1,4-87,1	0,007
Sexo							
Mujer	93,8	87,2	83,1	65,3	65,3		
Varón	94,4	94,4	91,0	47,9	31,9	0,7-4,1	0,21
Tiemp. a Dco.							
≤ 3 mes	95,2	89,9	86,7	56,8	56,8		
> 3 mes	92,6	92,6	88,2	56,1	46,8	0,6-3,4	0,41
Tamaño							
≤ 9 cm	97,1	94,2	91,1	79,9	70,8		
> 9 cm	91,1	87,6	87,6	33,7	33,7	1,2-8,5	0,02
Mitosis							
≤ 9	100	96,6	93,0	45,3	45,3		
> 9	83,8	77,4	77,4	67,8	67,8	0,4-3,5	0,74
Ganglios							
No	96,6	93,0	91,0	55,7	50,6		
Sí	76,2	76,2	76,2	61,0	61,0	0,4-5,3	0,49
Metástasis							
No	100	97,7	97,7	76,9	70,5		
Sí	82,9	77,4	71,5	0	0	3,6-37,1	0,001

Análisis univariante. Tiempo de supervivencia según variables

Ajuste multivariante (factores pronóstico independientes de riesgo):

	HR
Metástasis	11,4
Edad > 50	10,5

HR: hazard ratio



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