



Original article

Predictive factors of long-term colorectal cancer survival after ultrasound-controlled ablation of hepatic metastases[☆]



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ABSTRACT

Background and objective: The risk factors associated to long-term survival were assessed in patients with liver metastases of colorectal carcinoma undergoing ablative therapies.

Patients and methods: Single-centre cohort study, retrospectively analyzed and prospectively collected consecutive patients with unresectable metastatic liver disease of colorectal carcinoma treated with ablative therapies between 1996 and 2013. Factors associated with survival time were identified using Cox's proportional hazard model with time-dependent covariates. A forward variable selection based on Akaike information criterion was performed. Relative risk and 95% confidence intervals for each factor were calculated. Statistical significance was set as $p < 0.05$.

Results: Seventy-five patients with liver metastases of colorectal cancer, with a mean age of 65.6 (10.3) underwent 106 treatments. Variables selected were good quality of life (RR 0.308, 95% CI 0.150–0.632) and tumour extension (RR 3.070, 95% CI 1.776–5.308). The median overall survival was 18.5 months (95% CI 17.4–24.4). The survival prognosis in median was 13.5 vs. 23.4 months for patients with and without tumour extension, and 23.0 vs. 12.8 months for patients with good and fair or poor quality of life, respectively.

Conclusions: Good quality of life and tumour extension were the only statistically significant predictors of long-term survival in patients of colorectal carcinoma with liver metastatic disease undergoing ablative treatment with ultrasound.

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Factores predictivos de supervivencia a largo plazo del cáncer colorrectal tras la ablación de metástasis hepáticas con control ultrasonográfico

RESUMEN

Antecedentes y objetivo: Se evaluaron los factores de riesgo asociados a supervivencia a largo plazo en pacientes con metástasis hepáticas de carcinoma colorrectal sometidos a tratamientos ablativos.

Pacientes y métodos: Estudio de cohorte unicéntrico, retrospectivo, analizando los pacientes consecutivos y prospectivamente, presentando metástasis hepáticas no resecables de carcinoma colorrectal, siendo tratados con procedimientos ablativos entre 1996 y 2013. Los factores asociados a supervivencia fueron identificados utilizando el modelo de Cox de riesgo proporcional con covariables dependientes del tiempo. También se realizó una selección de variables con el criterio de información de Akaike. Se calcularon el riesgo relativo y los intervalos de confianza al 95% para cada factor. La significación estadística se estableció en $p < 0,05$.

Palabras clave:

Técnicas de ablación

Neoplasias colorrectales

Neoplasias del hígado

Calidad de vida

Ecografía intervencionista

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Resultados: Setenta y cinco pacientes con metástasis hepáticas de cáncer colorrectal, con una edad media de 65,6 (10,3) años, fueron sometidos a 106 tratamientos. Las variables seleccionadas fueron: extensión tumoral (RR 3,070, IC 95% 1,776–5,308) y buena calidad de vida (RR 0,308, IC 95% 0,150–0,632). La mediana de supervivencia global fue de 18,5 meses (IC 95% 17,4–24,4) y la mediana de pronóstico de supervivencia, de 13,5 frente a 23,4 meses para pacientes con y sin extensión del tumor, y de 23 frente a 12,8 meses para pacientes con buena y regular o mala calidad de vida, respectivamente.

Conclusiones: La extensión tumoral y la buena calidad de vida fueron los únicos factores predictivos estadísticamente significativos de supervivencia a largo plazo en pacientes con carcinoma colorrectal con metástasis hepáticas sometidos a tratamiento ablativo con control ultrasonográfico.

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Introduction

The liver is the most common site of metastasis in colorectal cancer.¹ Up to 25% of colorectal carcinomas develop liver metastasis as the first sign of disease, and half of the remaining patients will develop metastatic liver disease within 5 years.¹ In addition, metachronous liver metastases are observed in 40–50% of patients after resection of the primary colorectal tumor.² Only 8–27% of patients with liver-confined metastasis have potentially resectable tumours and most of the remaining patients rarely survive more than 5 years.³ The presence of liver metastasis also plays a crucial role in the prognosis of patients with colorectal cancer.

Proactive approaches have led to increased rates of liver resection in patients with potentially resectable tumours.⁴ However, several recent studies have shown that less invasive procedures such as local ablation techniques are also effective for treating primary and secondary liver metastasis, contributing to improved long-term survival.^{5–7}

The percutaneous ethanol injection (PEI) was one of the first effective ablation treatments described for small hepatocellular carcinomas in cirrhotic patients.⁸ Ethanol causes dehydration and necrosis in tumour cells, accompanied by small vessel thrombosis, leading to ischaemia and tumour destruction. Today, ultrasound (US) guided ethanol injections remain suitable for ablating small liver lesions because of their relative ease of application, low cost and availability; likewise, they can be used in open procedures.^{9,10}

Radiofrequency ablation (RFA) uses a form of alternating electrical current to destroy interstitial tissue.¹¹ Cell death is the result of the irreversible coagulation of proteins, including enzymes, intranuclear proteins and DNA protein. By placing the device inside the target tumour, both this and the surrounding liver are thermally destroyed. US is used during percutaneous, laparoscopic or open RFA procedures.¹² The combination of RFA and PEI may be beneficial in selected patients, allowing the treatment of larger liver lesions and limiting the complications that would arise if each technique was used individually.^{13,14}

However, experience with the use of the RFA, PEI or both in everyday practice is still a matter of research. The objective of this study was to assess the risk factors associated with long-term survival in patients with hepatic metastases from colorectal cancer undergoing RFA and/or ablation therapy with ethanol injection guided by US.

Patients and methods

Patients

We retrospectively analyzed all patients diagnosed consecutively at our site, with histologically confirmed liver metastasis or recurrences of unresectable metastatic colorectal cancer, who underwent US-guided ablation therapy with RFA and/or percutaneous ethanol injection or by open procedures, prospectively studied between 1996 and 2013. All patients included in the study

received a first ablation therapy. They were then subjected to periodic check-ups and eventually underwent a new ablation therapy. The study protocol was approved by the institution's Clinical Research Ethics Committee and written informed consent was obtained from all patients.

Procedure

Before the procedure, all tumours were located and measured by ultrasound with or without contrast, with biphasic study of computed tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI). Ablative treatment was exclusively guided by ultrasound in all detected liver metastases. Intraoperative US was used in patients undergoing open procedures¹⁵ and all tumours non-resected surgically were treated intraoperatively with ultrasound-guided ablation therapy. Ultrasound contrast has also been used in all patients in recent years due to the high detection rate compared with intraoperative US alone or combined with CT/MRI.¹⁶

Ethanol injection, RFA or both were performed percutaneously or intraoperatively according to previously described techniques.^{8,9,11} Ethanol ablation was performed using a multiple-hole 21-gauge needle with a conical tip (PEIT, Ethanoject needle, TSK, Tokyo, Japan). 3 types of RFA devices were used with different electrode designs, according to manufacturer. These were 1500X (Rita Medical Systems, Mountain View, Calif., USA), RF2000™ (Radiotherapeutic, Mountain View, Calif., USA) and Cool-tip™, RF ablation system (Covidien Tyco Healthcare Group LP, Valleylab, Boulder, Connecticut, USA). Patients were studied immediately after the first ablation therapy with contrast-enhanced US, using first and second generation ultrasound contrast agents, including Levovist® (Schering, Berlin, Germany) and SonoVue (Bracco Spa, Milan, Italy).¹⁷ Twenty-four hours later a new US control was performed to assess complications. Patients were monitored one month after the procedure and then 3 and 6 months later. After this period, control was performed in 6-month intervals, using contrast-enhanced US or biphasic CT scan or MRI with contrast¹⁸ until June 2013, completion date of the study, or until the patient's death. Ablation therapy using contrast-enhanced US was considered successful when the tumour showed no enhancement during the arterial phase or wash-out during the portal phase or the late phase, with a margin of at least 10 mm for the entire circumference of the tumor.¹⁹

Objective and data collection

The study objective was to determine disease-free and overall survival in months of those patients being studied as well as the risk factors associated with these survivals.

The information collected in all patients included: demographic data; variables associated with the tumour; use of chemotherapy; time since diagnosis of metastatic liver disease until the first ablation therapy; tumour recurrence (classified as: no recurrence,

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