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REVIEW

# Current oncologic applications of radiofrequency ablation therapies

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## Abstract

Radiofrequency ablation (RFA) uses high frequency alternating current to heat a volume of tissue around a needle electrode to induce focal coagulative necrosis with minimal injury to surrounding tissues. RFA can be performed *via* an open, laparoscopic, or image guided percutaneous approach and be performed under general or local anesthesia. Advances in delivery mechanisms, electrode designs, and higher power generators have increased the maximum volume that can be ablated, while maximizing oncological outcomes. In general, RFA is used to control local tumor growth, prevent recurrence, palliate symptoms, and improve survival in a subset of patients that are not candidates for surgical resection. It's equivalence to surgical resection has yet to be proven in large randomized control trials. Currently, the use of RFA has been well described as a primary or adjuvant treatment modality of limited but unresectable hepatocellular carcinoma, liver metastasis, especially colorectal cancer metastases, primary lung tumors, renal cell carcinoma, boney metastasis and osteoid osteomas. The role of RFA in the primary treatment of early stage breast cancer is still evolving. This review will discuss the general features of RFA and outline its role in commonly encountered solid tumors.



**Key words:** Radiofrequency ablation; Hepatocellular carcinoma; Colorectal cancer liver metastasis; Lung cancer; Renal cell carcinoma

**Core tip:** We have described the technical aspects of radiofrequency ablation (RFA), advances in delivery mechanisms, indications for usage, and its equivalence or lack of equivalence to surgical resection. We emphasized studies that reported long term oncologic outcomes associated with RFA use for primary and metastatic liver and lung tumors, and described the evolving role of RFA for breast and solid renal tumors.

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## INTRODUCTION

Surgical resection of all malignant cells remains the gold standard for treatment of most solid tumors[1]. However, surgical resection is not always an option in patients with coexistent morbidities or poor functional status where

resection would be associated with a high morbidity and mortality. As a result, a variety of local ablative methods, including chemical (ethanol, acetic acid, hot saline) and thermal (radiofrequency ablation, microwave ablation, laser ablation, cryoablation), have been developed to destroy cancer cells *in situ*. Radiofrequency ablation (RFA) has risen to the forefront amongst these local ablative modalities due to refinements in technology that maximize effectiveness and simplicity of use while minimizing associated morbidity. RFA is now used in the treatment, both curative and palliative, for solid tumors throughout the body. This minimally invasive technique can serve both as treatment for patients who are not surgical candidates, as well as an adjunct to surgery, facilitating resection or in combination with surgery achieving total tumor burden control.

## TECHNICAL FEATURES OF RFA

RFA uses radiowaves, which are of low frequency (460-480 kHz) and long wavelength, to generate heat within a tumor mass causing thermal coagulative necrosis. RFA differs from other local methods in that the electrode itself does not supply the heat. Needle electrodes supply an alternating electric current, which travels from the electrode to a grounding pad (monopolar) or between two electrodes (bipolar). As the ions within the tissue attempt to follow the alternating path of the current, ionic agitation creates frictional heat. This friction heats the surrounding tissue to 50-100 ℃, inducing instantaneous coagulative necrosis. Temperatures greater than 100 ℃ result in tissue desiccation and charging with loss of ions thus stopping current flow. This leads to a sudden rise of impedance[2], thus limiting the volume of tissue that can be successfully ablated.

The energy from the electrode tip produces a temperature that is proportional to the square of the radiofrequency current, which in turn decreases as the square of the diameter from the electrode[2]. Larger tumors require overlapping spheres, which increases the risk of incomplete necrosis and, therefore, local recurrence. Over the past several years, advances in delivery mechanisms that can either increase the amount of energy deposited or the conduction of heat through the tissue have increased the sphere of tissue that can be ablated[3]. There are currently five companies that produce commercially available RFA systems, four of which are approved by the Food and Drug Administration and available in the United States[4]. The specifications of each system are presented in Table 1.

Multiprobe array electrodes, in which multiple tines apply current simultaneously, achieve coagulation zones of 3-5 cm. Internally cooled (or cool-tip) electrodes also allow for greater ablation volumes. While it seems paradoxical to cool the electrode with a continuous infusion of fluid within the lumen, this cooling results in no local charring around the uninsulated electrode tip, thus allowing longer flow of current. Longer duration of current flow allows for a larger volume of local tissue coagulation, compared to non-internally cooled electrodes. Wet electrodes using saline (either isotonic or hypertonic) infused through the electrode into surrounding tissue, increase conductivity with greater amounts of infusion of ions in the tissue, increasing current flow and thus allowing longer duration of current flow and increasing volume of coagulation.

Several strategies have been developed to decrease tumor tolerance to heat and increase the effectiveness of thermal ablative techniques. The "heat-sink" effect created by proximity of tumors to large vessels that can dissipate heat is a primary mechanism by which the extent of thermal injury can be limited[5,6]. The Pringle maneuver, which involves occluding portal inflow during open RFA. This has been shown to improve volume of tissue (tumor) coagulation by increasing local heat deposition, rather than having heat being dissipated in the portal vein[6,7]. Tissue damage from chemotherapy and hypoxic injury to tumors cells from embolization have also been shown to increase tumor sensitivity to hyperthermia. A synergistic effect between neoadjuvant transarterial chemoembolization and RFA in the treatment of hepatocellular carcinoma has also been demonstrated[7].

### *RFA technique*

RFA can be performed percutaneously, or during laparoscopic or open surgery. There are advantages and disadvantages to each, and the approach will depend on the condition of the patient, tumor characteristics such as location, size, number and growth pattern, and experience and preference of the provider[8]. There is insufficient evidence as of date indicating which delivery method is the preferred due to a lack of randomized control trials and varying patient and tumor characteristics between single technique studies. In a study comparing open, laparoscopic, and percutaneous approaches for liver tumors, there was no difference in mortality, major complications, or overall survival; but open compared to percutaneous approach resulted in improved disease free survival and decreased local tumor recurrence[9].

The percutaneous approach has the advantage of being performed under conscious or deep sedation, providing an option for patients who are higher surgical risk. This can usually be done as an outpatient or with a very short hospital stay, and can be performed multiple times if needed. The percutaneous approach can also be performed under anesthesia. Other advantages of this technique are the use of sonographic, computed tomography (CT) or magnetic resonance imaging (MRI) to guide precise electrode placement. At the same setting, contrast enhanced sonography or contrast enhanced CT can be done during the procedure to check for adequacy of ablation. Disadvantages of the percutaneous technique are lack of visualization of small surface tumors or deeper tumors which can be better identified with the

**Table 1 Radiofrequency ablation systems commercially available in the United States[4,8]**

| RFA system | Electrodes | Generator power/ frequency | Control system | Algorithm used to maximize volumes |
|---|---|---|---|---|
| Boston scientific | 14 gauge, 10-12 tines, umbrella shaped | 200 W/460 kHz | Impedance controlled | Coaxial system |
| Valleylab (radionics) | 17.5 gauge, single cooled needle or three cooled needles in triangular cluster | 200 W/480 kHz | Impedance controlled | Cool-tip |
| RITA medical systems | | 250 W/460 kHz | Temperature controlled | |
| Starburst XL | 14 gauge, 9 tines, Christmas tree shape max diameter 5 cm | | | Expandable |
| Starburst XLi | 14 gauge, 9 tines, max diameter 7 cm | | | |
| Starburst Flex | 13 gauge, flexible | | | Expandable, wet electrode |
| Berchtold | 18-14 gauge | 60 W/375 kHz | Impedance or temperature controlled | Wet electrode |

Modified from[4,8]. Cool-tip: Cooled electrode achieved with chilled water flowing through electrode but not entering tissue; Wet-electrode: Saline infusion into tissue adjacent to electrode creates larger "virtual" electrode around metal electrode tip.

open technique. Percutaneous RFA has shown excellent results for small < 3 cm neoplasms in the liver, lung or kidney. However, higher local recurrence has been shown with the percutaneous approach for larger tumors[10] and tumors in close proximity to major vessels, such as the portal vein.

Open RFA allows for better visualization and the ability to manipulate adjacent structures. It has the advantage of being able to detect occult metastatic disease with use of intra-operative ultrasound (US) and allows for treatment within a greater anatomic range. With hepatic RFA, another advantage is the ability to occlude portal inflow (Pringle maneuver) which, as described above, reduces heat dissipation and, therefore, increases the volume of tissue ablated. This technique is particularly valuable when tumors are located in proximity to vascular structures.

Laparoscopic RFA combines many of the benefits of both the percutaneous and open approaches. It is minimally invasive with less morbidity of a large incision while still allowing better visualization of the tumor and of adjacent structures to optimize staging. Pneumoperitoneum may also work in a similar manner to the Pringle maneuver and decrease the heat sink effect in tumors in proximity to large vessels by decreasing portal flow[11]. It also allows resection or displacement of structures adjacent to tumors that cannot be performed with the percutaneous technique.

### Imaging

Imaging plays an important role in the diagnosis and localization of the tumor, in real-time monitoring of the ablation zone, in assessment of tissue response to RFA therapy, and finally in patient follow-up. The RF probe is usually placed under CT or US guidance, and the RFA procedure monitored with real-time US. Ablation zones are seen on US as hyperechogenic areas which represent microbubbles created from the vaporization of interstitial fluid from ablated tissue. However, these hyperechogenic areas do not completely parallel the ablated zone. To determine the extent of necrosis following RFA in countries outside of the United States, US contrast is used at the time of the procedure to check for complete ablation and whether re-treatment is needed at the setting[12]. In the United States, a follow-up contrast-enhanced CT or MR is typically used, with successfully ablated areas failing to enhance. A thin enhancing rim representing either inflammation or hemorrhagic granulation tissue may surround the ablated zone for several weeks following treatment[13]. Follow-up may be done with CT, MRI or positron emission tomography scan, depending on the type, size and location of tumor.

The goal of RFA is usually to ablate 1 cm margin of normal tissue surrounding the tumor on all sides[8,14,15]. This surgical margin is necessary because of the difficulty of accurately determining the extent of the coagulation zone, and because of the possibility of microscopic malignancy surrounding the gross tumor[8]. Exceptions to the 1 cm margin rule may include organs such as the kidney, in which preservation of normal renal parenchyma would be a priority, or when tumor debulking for palliation or relief of neuroendocrine symptoms is the goal of treatment or when surrounding vital structures limit the extent of ablation.

### Complications

RFA has been shown to be a relatively safe procedure, with mortality between 0.3% and 0.8% and morbidity 2% and 10%[16,17]. Complications include post-procedural pain, post-RFA syndrome with fever and flu-like symptoms that usually resolves within the first 24 h, skin burns from improperly placed grounding pads, thermal injury to adjacent structures, bleeding, secondary infection, and tumor seeding, which can be prevented by cauterization of the needle tract on withdrawal of the probe[8].

## SOLID TUMOR ABLATIVE EXPERIENCE

### Liver

The most extensive body of literature on RFA for the treatment of solid tumors involves its use with hepatic malignancies, both primary and metastatic. Currently, RFA is considered a first line treatment modality for local control of hepatocellular carcinoma in patients with

**Table 2 Studies reporting survival after use of radiofrequency ablation for colorectal liver metastases**

| Ref. | Patients (tumors) *n* | Median tumor size (cm) | Extra-hepatic disease | Chemotherapy | Method | % complete ablation | Local recurrence | Overall survival | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 1 yr | 3 yr | 5 yr |
| Abdalla *et al*[26] | 57 (110) for RFA | 2.5 | No NR | 0 | NR | 9% for RFA | NR | 37% for RFA | | NR |
| | | | | | | | | 43% for HR + RFA | | |
| | 190 for HR | | | | | 5% for HR + RFA | | 73% for HR | | |
| | 101 for RFA + HR | | | | | 2% for HR | | | | |
| Siperstein *et al*[27] | 234 (665) | 3.9 (mean) | Yes | 80% before RFA | L | NR | NR | NR | 20%[2] | 18%[2] |
| Park *et al*[28] | 30 for RFA | 2.0 for RFA | No | 73% after RFA | P | NR | 23% for RFA | NR | NR | 19%[2] for RF1 |
| | 59 for HR | 3.1 for HR | | 81% after HR | | | 2% for HR | | | 48%[2] for HR |
| Abitabile *et al*[54] | 47 (147) | 2 | Yes | After RFA | O, P | 97% | 9% for overall | 88%[1] | 57%[1] | 21%[1] |
| | | | | | | | 0%-5% for < 3 cm | | | |
| Gillams *et al*[55] | 167 (167) | 3.9 (mean) | Yes | 80% before RFA | P | NR | 14.00% | 99%[1] | 58%[1] | 30%[1] |
| | | | | | | | | 91%[2] | 28%[2] | 25%[2] |
| Jakobs *et al*[56] | 68 (183) | 2.28 (mean) | No | 78% parallel or after | P | NR | 18.00% | 96%[2] | 71%[2] | |
| Machi *et al*[57] | 100 (507) | 3.0 (mean) | NR | | O, L, P | | 7% | 90% | 42% | 31% |
| Schindera *et al*[58] | 14 (20) | 1.8 | No | NR | P | 89% | 15% | 72%[2] | 60%[2] | NR |
| White *et al*[59] | 30 (56) | 3.0 (0.8-7) | No | 36% before, 50% after | P | 89% | 17% | 75%[2] | 45%[2] | NR |
| Solbiati *et al*[60] | 117 (179) | 2.6 | Yes | 72% parallel | P | 98% | 39% | 93%[2] | 46%[2] | NR |

[1]Calculated from time of diagnosis of liver metastases; [2]Calculated after radiofrequency ablation (RFA) treatment of liver metastases. P, L, O: Percutaneous, laparoscopic, open; NR: Not reported; HR: Hazard ratio.

Child-Pugh B or higher cirrhosis where resection would have a higher associated mortality. It is indicated in patients with 3 or fewer tumors that are 3 cm or smaller (Milan criteria)[18]. It has recently been shown to be superior to percutaneous ethanol injection with regards to survival and local recurrence[19]. It's equivalence to surgical resection in patients who satisfy the Milan criteria remains controversial. A prospective randomized trial and a large retrospective analysis comparing local ablative techniques with surgical resection for patients with small solitary tumors, stage T1, found no difference in overall survival between RFA and surgical resection[20-22]. Smaller observational studies have demonstrated similar results[11]. A meta-analysis comparing RFA to hepatic resection in all subsets of patients found improved 3 and 5 year overall and disease free survival and decreased local recurrence in patients who underwent hepatic resection[23]. However, in patients with tumors smaller than 3 cm, the overall survival was comparable. In patients with larger tumors (> 3 cm), the combination of chemoembolization with RFA has been demonstrated to be superior to RFA alone in improving survival[24,25]. This is based on the hypothesis that RFA results in a zone of inflammation that can then be strategically used for targeted delivery of chemotherapeutic agents *via* chemoembolization.

The majority of the literature regarding hepatic metastases comes from single arm, retrospective or prospective studies evaluating RFA for treatment of unresectable colorectal metastases. In such studies, hepatic resection is superior to both RFA alone or combination of RFA with hepatic resection in regards to local recurrence and overall survival[26]. However, during open resection, additional tumors may be detected on the liver surface or deep metastases may be seen with intra-operative US. These additional lesions can be resected or treated with intra-operative RFA. Randomized control trials directly comparing RFA to hepatic resection for resectable disease have yet to be performed.

There is considerable overlapping variability in the 5 year survival and the local recurrence rates due to differences in definition of local recurrence, inclusion criteria for unresectability, extent of extrahepatic disease, and patient and tumor characteristics between the studies. Local recurrence rates varied between 9% and 40% and 5 year overall survival varied between 18% and 30% (Table 2). The best outcomes were in patients with solitary tumors less than 3 cm and slightly less in patients with 3 or fewer tumors less than 3 cm[27]. Local recurrence was significantly larger in patients with tumors between 3-5 cm[20]. Retrospective studies comparing hepatic resection to RFA for patients who were potentially resectable but poor candidates for surgery due to co-morbidities or refusal, demonstrated decreased local recurrence and improved overall survival with hepatic resection[28]. Therefore it is evident that surgical resection remains the gold standard; but for those who are not candidates for surgery, an alternative such as RFA is valuable.

### Lung

RFA is increasingly being applied to malignant lung nodules for local control as well as for palliation as its feasibility and efficacy is becoming more established in the literature. Surgical resection remains the gold standard for curative treatment of primary lung cancers and malignant metastasis. However, only about 30% of

**Table 3 Studies involving survival using radiofrequency ablation for primary lung tumors and metastases**

| Ref. | Patients (tumors) *n* | Mean tumor size (cm) | Tumor type | Median local progression free interval | Overall survival | | | Complications |
|---|---|---|---|---|---|---|---|---|
| | | | | | 1 yr | 2 yr | 3 yr | |
| Ambrogi *et al*[1] | 54 (64) | 2.4 | 40 for NSCLC<br>24 for Mets | < 3 cm - 15.8 mo<br>> 3 cm - 6.6 mo | 72% for NSCLC[1]<br>88% for Met[1] | 46% for NSCLC[1]<br>72% for Mets[1] | 30% for NSCLC[1]<br>NR for Mets[1] | 6 for PTX<br>1 for chest wall hematoma |
| Kim *et al*[30] | 8 for RFA<br>14 for SR | 3.66 for RFA<br>3.99 for SR | All stage I NSCLC | NR | 88% for RFA<br>93% for SR | 50% for RFA<br>77% for SR | 25% for RFA<br>67% for SR | 1 for PTX<br>4 for hemoptysis |
| Simon *et al*[35] | 153 (189) | 2.7 | 75 for stage I NSCLC<br>57 for Mets | < 3 cm - 45 mo<br>> 3 cm - 12 mo | 78% for NSCLC<br>70% for Met | 57% for NSCLC[1]<br>54% for Mets[1] | 36% for NSCLC[1]<br>44% for Mets[1] | 18 for PTX<br>5 for hemoptysis<br>4 for death |
| Chua *et al*[37] | 148 | 4 | 108 for CRCM<br>Other<br>40 for Mets | 11 mo | NR | NR | 60% | 66 for PTX<br>16 for pleural effusion<br>1 for vleeding |
| Lencioni *et al*[61] | 106 (183) | 3.5 | 33 for NSCLC<br>73 for Mets | NR | 70% for NSCLC<br>89% for CRCM<br>92% for Other | 48% for NSCLC<br>66% for CRCM<br>64% for Other | | 27 for PTX<br>4 for effusion |
| Yan *et al*[62] | 55 | 2.1 | All CRCM | NR | 85% | 64% | 46% | 16 for PTX/<br>9 requiring drainage<br>5 for hemoptysis |
| Hiraki *et al*[63] | 20 | 2.4 | All stage I NSCLC | 9 mo | 90% | 84% | 74% | 13 for PTX/<br>1 requiring drainage |

[1]Calculated based on Kaplan-Meier survival curves. NR: Not reported; NSCLC: Non-small cell lung cancer; CRCM: Colorectal cancer metastasis; Mets: Other tumor metastases; PTX: Pneumothorax; SR: Surgical resection; RFA: Radiofrequency ablation.

patients with primary lung cancer are eligible for surgery at the time of diagnosis due to poor functional status and chronic obstructive pulmonary disease[29]. In patients with pulmonary metastasis, multiple lesions and advanced stage usually precludes curative surgical resection.

Currently, there is insufficient evidence to prove that RFA is comparable to surgical resection. There are currently no prospective randomized controlled trials comparing RFA with standard surgical treatment options in patients with malignant lung nodules. Data is limited to case series with differences in number of primary and secondary lung lesions, criteria for unresectability, number of prior resections, history of prior radiation therapy, differences in follow-up protocols, and criteria for determining extent of response to RFA treatment.

However, a small matched case series of 22 patients comparing RFA to resection in patients with stage I non-small cell lung cancer (NSCLC) demonstrated comparable survival in RFA patients at 1, 2, and 5 years[30]. The RAPTURE study, a large prospective multicenter single arm trial, using RFA in patients with early stage NSCLC or lung metastases demonstrated 1 and 2 year overall survival rates of 70% and 48% respectively in patients with primary lung tumors, and 89% and 66% 1 and 2 year overall survival in patients with colorectal metastases. The cancer specific survival was higher in both groups; 92% and 73% at 1 and 2 years in the NSCLC cohort and 91% and 68% in the cohort with colorectal metastases.

The 1, 2, 3 year overall survival for patients with early stage primary lung cancer treated with RFA varies from 70% to 90%, 48% to 84%, 25% to 74%, respectively (Table 3). This is comparable to the 1, 3, 5 year overall survival of patients who undergo lobectomy or segmental resection for early stage lung cancer[31-34]. In most studies that compare outcomes based on size of tumor ablated, patients with tumors smaller than 3 cm had longer median progression free intervals and overall survival[35].

The median procedure related morbidity and mortality are 37.5% and 0% respectively[36]. The majority of complications from thoracic RFA are minor with the most frequently encountered being pneumothorax and pleural effusions (4.5%-61%) and hemoptysis. Others include pain, fever and pneumonia. Despite the high incidence of pneumothorax, only a minority, 11%, require pleural drainage[36]. The incidence of pneumothorax increases as the number of lesions ablated[37].

### Breast

The role of RFA in breast cancer is still emerging. There is a growing trend towards breast conservation techniques that minimize scarring, breast deformity, and improve overall post procedure cosmesis. Several small single institution studies have established the feasibility of RFA and outlined potential complications (Table 4). In majority of these studies, RFA was followed by lumpectomy or mastectomy, either immediately or in a delayed fashion. The procedure was done under local or general anesthesia depending on whether resection was delayed or followed immediately after RFA, respectively. Response was assessed by pre- and post-procedural MRI which correlated better with pathologic response than US[38]. HE staining, immunohistochemistry with CK 18/8, or nicotinamide adenine dinucleotide-diaphorase cell viability assay were used to assess histopathologic response. There

**Table 4 Studies involving survival using radiofrequency ablation for primary lung tumors and metastases**

| Ref. | Patients | Range tumor size (cm) | Mean tumor size (cm) | Complete coagulation necrosis *n* (%) | Resection | Assessment of cell viability | Complications |
|---|---|---|---|---|---|---|---|
| Burak *et al*[38] | 10 | 0.8-1.6 | 1.2 | 9 (90) | Delayed | HE CK8/18 | None |
| Singletary *et al*[40] | 29 | ≤ 2.0 | - | 25 (86) | Immediate | HE NADH-diaphorase | 1 skin burn |
| Oura *et al*[41] | 52 | 0.5-2.0 | 1.3 | 52 (100) | Delayed | NR | 1 skin burn |
| Khatri *et al*[64] | 15 | 0.8-1.5 | 1.28 | 13 (93) | Immediate | HE NADH-diaphorase | 2 skin puckering |
| Noguchi *et al*[65] | 10 | 0.5-2.0 | 1.1 | 10 (100) | Immediate | HE NADH-diaphorase | None |
| Fornage *et al*[66] | 20 | 0.6-2.0 | 1.2 | 21 (100) | Immediate | HE NADH-diaphorase | None |
| Hayashi *et al*[67] | 22 | 0.5-2.6 | 0.9 (median) | 19 (86) | Delayed | HE NADH-diaphorase | 1 skin burn |
| Izzo *et al*[68] | 26 | 0.7-3.0 | 1.8 | 25 (96) | Immediate | HE NADH-diaphorase | 1 skin burn |

NR: Not reported; HE: Hematoxylin and eosin stain; NADH: Nicotinamide adenine dinucleotide.

are several studies that have reported HE staining maybe inadequate to assess histopathologic response since it gives a broad spectrum of necrosis and that techniques that assess cell viability are better[38,39]. Complete coagulative necrosis was achieved in 80%-100% of the patients, with skin burn being the most common complication in a very small subset of patients.

Patient selection criteria were strict, including mostly patients with invasive tumors less than 2 cm in size; a few studies had a small portion of patient with non-invasive tumors. The presence of extensive intraductal component was also a relative contraindication to RFA. In addition, estrogen and progesterone receptor status, her 2 status, grade, histology, and need for chemotherapy had to be known prior to RFA since no residual tumor cells would be available post-procedure if 100% successful. Superficial tumors within 1 cm of the skin are a relative contraindication as well, due to increased risk for skin burns. Various strategies to minimize skin burns have been employed in the studies including cooling the breast with sterile ice packs and subcutaneous injection of sterile saline or a high resistance solution to displace the tumor away from the skin. In addition, preoperative chemotherapy is a contraindication since it can lead to an underestimation of tumor size and leave occult foci of residual carcinoma[40].

There are currently no studies comparing RFA to surgical resection, and no long term studies depicting local recurrence rates or survival in patients who receive RFA instead of surgical resection. Very few studies have evaluated RFA as an alternative to surgical resection. Oura *et al*[41] reported their experience treating 52 patients, with a mean tumor size of 1.3 cm (range 0.5-2.0 cm), with RFA following sentinel node biopsy. There was no local-regional or distant recurrence after an average 15-mo follow-up (range 6-30 mo).

Patient response to RFA has been favorable. Oura *et al*[41] retrospectively evaluated cosmetic results, which were found to be excellent in 43 patients (83%), good in 6 patients (12%) and fair in 3 patients (6%). The authors found that a major factor leading to poor cosmesis was mass formation at the site of RFA, especially in women with small breasts. This can lead to increased patient anxiety as well.

Progress in the application of RFA for breast tumors is at present hampered by our ability to accurately judge the margin status which is a critical variable in local recurrence rate. Evolution in imaging technology will foster such advancements. Nonetheless, as more breast cancers are being diagnosed at a smaller size, a focused image-guided ablation can minimize destruction of normal breast tissue and thus may positively impact cosmesis.

### Kidney

As with other solid tumors, RFA is increasingly being applied for the therapy for renal tumors as less invasive and nephron-sparing techniques, including partial nephrectomy and laparoscopic nephrectomy, have proven to have comparable 5-year and disease-free survival[42].

Currently, RFA as primary treatment for renal malignancy is limited in study to a select group of patients with early T1a disease or for whom surgical resection is not an option. These include patients with only one kidney, multifocal disease, Von Hippel Lindau, limited renal function, elderly patients or patients with comorbidities that are poor candidates for surgery[8,43-45]. Contraindications include a life expectancy less than one year, the presence of distant metastases, tumors > 5 cm, or tumors in the hilum or central collecting system. Studies have consistently shown 91%-97% complete first ablation success for small (< 3-4 cm), exophytic, peripherally located tumors (Table 5). This is due to the fact that peripherally located tumors are surrounded by peri-renal fat that provides insulation, allowing the high temperatures necessary for successful ablation to be achieved. Conversely, hilar blood flow creates a heat-sink effect making treatment of central tumors more challenging. The recurrence free survival varies from 79%-91% in biopsy proven renal cell cancers, while the 3 and 5 year cancer specific survival ranges from 95%-100% in the few long term studies.

### Bone tumors and metastatic bone lesions

RFA has been long proven efficacious for the treatment of osteoid osteomas. It is performed in patients with typical clinical and radiographic characteristics of an osteoid osteoma (radiolucent nidus surrounded by reactive sclerosis) for treatment of bone pain. It is successful initially in 73%-98% of patients with 92%-100% secondary

**Table 5 Studies involving survival after radiofrequency ablation for solid renal tumors**

| Ref. | Patients (tumors) *n* | Method | Mean tumor size (cm) | RCC | Complete first ablation | Recurrence free survival | Overall survival (yr) | | | Cancer specific survival (yr) | | Complications |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 1 | 3 | 5 | 3 | 5 | |
| Tracy *et al*[69] | 208 (243) | P, L, O | 2.4 | 79% | 97% | 90% at 3 yr[2] | 99%[1] | 93%[1] | 85% | 95% for RCC | 99% for RCC | NR |
| Levinson *et al*[70] | 31 (34) | P, L | 2.1 | 58% | 91% | 80% at 5 yr[2] | NR | NR | 63% for all[3]<br>58% for RCC[4] | NR | 100% for all<br>100% for RCC | 4 for perinephric hematoma ;<br>1 for liver burn;<br>1 for death from pneumonia |
| Zagoria *et al*[71] | 41 (48) | P | 2.6 | 100% | NR | 88% at 5 yr | NR | NR | 66% | NR | NR | 2 for pneumothorax no drainage;<br>2 for ureteral strictures |
| Stern *et al*[72] | 40 | P, L | 2.4 | 81% | 97% | 91% at 3 yr[2] | NR | NR | NR | 100% for RCC | NR | 2 for minor; 3 for major |

[1]Calculated based on Kaplan-Meier curve and life table; [2]In biopsy proven renal cell carcinoma (RCC); [3]80 mo overall survival; [4]57 mo overall survival. P, L, O: Percutaneous, laparoscopic, open; NR: Not reported.

success rates and majority of patients experiencing pain relief within the first 1-2 wk of treatment[46-49]. Complication rates are minimal with skin necrosis and burns being the most common. It has been demonstrated to be comparable to surgical resection with regards to recurrence[50]. RFA has also been described in case reports for the treatment of other benign bone tumors.

More recently, RFA has been applied as a palliative modality for the treatment of painful metastatic bone lesions. External beam radiation remains the gold standard for treatment of localized bone pain from a metastatic focus. However, 20%-30% of patients don't respond and are recalcitrant to pharmacotherapy[51,52]. In addition, patients previously irradiated at a recurrent site, may not be eligible for repeat radiation therapy. Ninety percent to ninety-five percent of patients treated with RFA experience a clinically significant reduction in pain that can been seen within the first week of treatment lasting up to 24 wk[52,53]. Complication rates are minimal and can vary from bleeding, pathologic fractures, skin and muscle burns and damage to adjacent neurovascular structures[46].

## CONCLUSION

RFA has been demonstrated to be an effective local ablative technique in patients with a variety of solid tumors. More prospective randomized studies are needed before RFA will replace surgical resection for small, limited tumors involving the lung or liver. Long term studies establishing its oncological effectiveness in breast and solid renal tumors are still needed. The future of thermal ablative techniques may or may not involve radiofrequency waves as newer ablative techniques involving microwaves are currently being developed which offer the advantages of higher intratumoral temperatures, larger ablative volumes, and faster ablation times while minimizing energy dissipation. However, the safety and efficacy of microwave ablation is still under evaluation. Regardless of the ablative technique, proper patient selection remains a key factor in determining who will most likely benefit.

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BRIEF ARTICLE

# Prognostic factors in resectable cholangiocarcinoma patients: Carcinoembryonic antigen, lymph node, surgical margin and chemotherapy

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## Abstract

**AIM:** To evaluate outcomes in resectable cholangiocarcinoma patients and to determine prognostic factors.

**METHODS:** A retrospective study was conducted among newly-diagnosed cholangiocarcinoma patients from January 2009 to December 2011 who underwent curative resection in Srinakarind Hospital (a 1000-bed university hospital). Two hundred and sixty-three cholangiocarcinoma patients with good performance were enrolled. These patients had pathological reports with clear margins or microscopic margins. Prognostic factors which included clinical factors, serum liver function test as well as serum tumor makers at presentation, tumor data, and receiving adjuvant chemotherapy were determined by uni- and multivariate analysis.

**RESULTS:** The median overall survival time was 17 mo (95%CI: 13.2-20.7); and 1-, 2-, and 3- year survival rates were 65.5%, 45.2% and 35.4%. Serum albumin levels, serum carcinoembryonic antigen (CEA) levels, staging classifications by American Joint Committee on cancer, pathological tumor staging, lymph node metastases, tumor grading, surgical margin status, and if adjuvant chemotherapy was administered, were shown to be significant prognostic factors of resectable cholangiocarcinoma by univariate analysis. Multivariate analysis, however, established that only abnormal serum CEA [hazard ratio (HR) 1.68; $P$ = 0.027] and lymph node metastases (HR 2.27; $P$ = 0.007) were significantly associated with a decrease in overall survival, while adjuvant chemotherapy (HR 0.71; $P$ = 0.067) and surgical margin negative (HR 0.72; $P$ = 0.094) tended to improve survival time.

**CONCLUSION:** Serum CEA and lymph node metastases which were associated with advanced stage tumors become strong negative prognostic factors in cholangiocarcinoma.



**Key words:** Cholangiocarcinoma; Prognosis; Carcinoembryonic antigen; Lymph nodes; Neoplasm metastasis; Surgical margin status; Hepatectomy; Chemotherapy; Adjuvant; Survival rate

**Core tip:** Cholangiocarcinoma has a high prevalence in the Asian countries, particularly Thailand. Cholangiocarcinoma patients usually have a high mortality rate and poor treatment outcomes. Curative surgery is the only treatment for early stages of this cancer. Cholan-

giocarcinoma has a high rate of recurrence. This study aimed to evaluate outcomes in resectable cholangiocarcinoma patients and to determine prognostic factors. The results demonstrated serum carcinoembryonic antigen and lymph node metastases which were associated with advanced stage tumors become strong negative prognostic factors in cholangiocarcinoma, while additional treatment including adjuvant chemotherapy and adequate surgical resection may improve survival time.

Wirasorn K, Ngamprasertchai T, Chindaprasirt J, Sookprasert A, Khantikaew N, Pakkhem A, Ungarereevittaya P. Prognostic factors in resectable cholangiocarcinoma patients: Carcinoembryonic antigen, lymph node, surgical margin and chemotherapy. *World J Gastrointest Oncol* 2012; 5(4): 81-87 Available from: URL: http://www.wjgnet.com/1948-5204/full/v5/i4/81.htm DOI: http://dx.doi.org/10.4251/wjgo.v5.i4.81

## INTRODUCTION

Cholangiocarcinoma is a malignant tumor of intrahepatic and extrahepatic bile duct epithelium[1]. It is a second most common malignancy of primary liver tumors worldwide[2]. The highest incidence is in the Northeast region of Thailand, while it is a rare tumor in Europe and America[3,4]. *Opisthorchis viverrini* infestation is a major risk factor in Thai patients, while primary sclerosing cholangitis, obesity, viral hepatitis B and viral hepatitis C infection are the risk factors in Western countries[5,6]. Cholangiocarcinoma is commonly classified into 3 groups based on the location of the tumor: intrahepatic, perihilar, or distal types[1].

Surgery with clear surgical margin is an important treatment for patients with local disease[7]. Standard surgery for cholangiocarcinoma depends on its location. Major hepatectomy is a surgical procedure for intrahepatic cholangiocarcinoma and perihilar cholangiocarcinoma, while pancreaticoduodenectomy is performed in distal cholangiocarcinoma[7,8].

Although most patients receive surgical treatment, the five-year survival rate is extremely low[9]. High locoregional recurrence and metastases are common causes of death in resectable patients[10]. Benefits of adjuvant therapy in achieving long-term survival in resectable cholangiocarcinoma patients are controversial[11]. Previous studies attempted to identify prognostic factors in this group[12-15]. Surgical margin status and lymph node involvement are important prognostic factors[9,11,16]. Other risk factors may be differentiation of tumor cells, preoperative tumor markers like carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA), and site of tumor[13,17,18]. Data about prognosis in resectable cancer patients, however, are still limited. Moreover, only a few participants were enrolled in former reports. Therefore, this study aimed to determine prognostic factors in cholangiocarcinoma patients who underwent curative resection.

## MATERIALS AND METHODS

### Patients

A retrospective study was conducted among newly-diagnosed, cholangiocarcinoma patients from January 2009 to December 2011, who underwent curative surgery in Srinakarind Hospital, Khon Kaen University (a 1000-bed university hospital), Khon Kaen, Thailand. The study was reviewed and approved by the institutional review board (HE 551183). Curative resection was defined as a total excision of the entire tumor, including the primary tumor and the associated lymph node drainage fields. Two hundred and sixty-three cholangiocarcinoma patients with good performance status were enrolled. All patients with curative resection had pathological reports with a negative surgical margin or microscopic surgical margin. Demographic data including sex, age, underlying disease especially type 2 diabetes mellitus, body weight, height, and clinical manifestations were collected. Body mass index (BMI) was calculated from weight in kilograms divided by the square of the height in meters (kg/m$^2$). BMI cutoffs were classified according to the World Health Organization criteria for Asian and Pacific populations (underweight, < 18.5 kg/m$^2$; healthy, 18.5-22.9 kg/m$^2$; at risk, 23-24.9 kg/m$^2$; obese Ⅰ, 25-29.9 kg/m$^2$; and obese Ⅱ, ≥ 30 kg/m$^2$)[19]. Preoperative liver function status including total bilirubin, cholesterol, alanine transaminase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), as well as serum tumor markers including CA 19-9 and CEA were evaluated.

Tumor data included tumor location, staging classification by the 7$^{th}$ edition of American Joint Committee on Cancer (AJCC), pathological tumor staging (pT), lymph node metastasis, tumor differentiation, and surgical margin status. All patients received the appropriate surgical procedure. Adjuvant chemotherapy was administered in patients who accepted the risk-benefit after a discussion with their physicians.

### Statistical analysis

The survival time was defined as date of diagnosis to date of death from any cause. Patients' characteristics and tumor data were summarized as mean and percentage. The cumulative survival rate is presented by the Kaplan-Meier curve. The following variable factors were analyzed: sex, age, diabetic status, hepatomegaly, BMI status, serum total bilirubin level, serum cholesterol level, serum albumin level, serum ALT level, serum AST level, serum ALP level, serum CEA level, serum CA 19-9 level, AJCC staging, tumor location, pT, lymph node status, tumor differentiation, surgical margin status and adjuvant chemotherapy. Differences in survival between subgroups were compared using the log-rank test. Univariate analysis was performed using the chi-squared testing. Multivariate analysis was performed with the Cox proportional hazard model. The statistical analyses were performed by using SPSS software version 20.0. A *P*-value of less than 0.05 was considered statistically significant. The database was closed for analysis in August 2012.

**Table 1 Baseline characteristics of 263 resectable cholangiocarcinoma patients *n* (%)**

| | |
|---|---|
| Age, yr | |
| mean ± SD | 59.0 ± 8.9 |
| Range | 35-80 |
| Male | 181 (69.6) |
| DM | 19 (6.5) |
| BMI (mean ± SD), kg/m$^2$ | |
| < 18.5 | 23 ± 8.7 |
| 18.5-22.9 | 127 ± 48.3 |
| 23-24.9 | 47 ± 17.9 |
| 25-29.9 | 48 ± 18.3 |
| ⩾ 30 | 13 ± 4.9 |
| Not available | 5 ± 1.9 |
| Clinical manifestation | |
| Abdominal pain | 164 (62.4) |
| Jaundice | 54 (20.5) |
| Fever | 6 (2.3) |
| Cholangitis | 4 (1.5) |
| Weight loss | 1 (0.4) |
| Asymptomatic | 17 (6.5) |
| Hepatomegaly | 153 (58.2) |
| Total bilirubin (mg/dL) | |
| < 10 | 213 (81.0) |
| ⩾ 10 | 50 (19.0) |
| Cholesterol (mg/dL) | |
| < 200 | 168 (63.9) |
| ⩾ 200 | 95 (36.1) |
| Albumin (g/dL) | |
| < 3 | 42 (16.0) |
| ⩾ 3 | 220 (83.7) |
| ALT (U/L) | |
| < 30 | 46 (17.5) |
| ⩾ 30 | 151 (82.5) |
| AST (U/L) | |
| < 30 | 25 (9.5) |
| ⩾ 30 | 238 (90.5) |
| ALP (U/L) | |
| < 100 | 82 (31.2) |
| ⩾ 100 | 180 (68.5) |
| CA 19-9 (U/mL) | |
| < 35 | 108 (41.1) |
| ⩾ 35 | 148 (56.3) |
| CEA (ng/mL) | |
| < 2.5 | 65 (24.7) |
| ⩾ 2.5 | 183 (69.6) |
| Receiving adjuvant chemotherapy | |
| Yes | 138 (52.5) |
| No | 125 (47.5) |

CA 19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; ALT: Alanine transaminase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; BMI: Body mass index; DM: Diabetes mellitus.

**Table 2 Tumor data of 263 resectable cholangiocarcinoma *n* (%)**

| | |
|---|---|
| Tumor location | |
| Intrahepatic | 166 (63.1) |
| Perihilar | 91 (34.6) |
| Distal | 6 (2.3) |
| AJCC staging | |
| 0 | 11 (4.2) |
| 1 | 37 (14.1) |
| 2 | 54 (20.5) |
| 3 | 89 (33.8) |
| 4 | 72 (27.4) |
| pT stage | |
| 0 | 10 (3.8) |
| 1 | 47 (17.9) |
| 2 | 85 (32.3) |
| 3 | 95 (36.1) |
| 4 | 25 (9.5) |
| pN stage | |
| 0 | 167 (63.5) |
| 1 | 96 (36.5) |
| Tumor grading | |
| Well diff | 198 (75.3) |
| Moderate diff | 14 (5.3) |
| Not available | 51 (19.4) |
| Margin surgical resection | |
| Free | 134 (51.0) |
| Not free | 129 (49.0) |

AJCC: American Joint Committee on Cancer; pN: Pathologic node; pT: Pathologic tumor.

## RESULTS

The patients' characteristics and tumor data are presented in Tables 1 and 2. Abdominal pain was the most common clinical presentation. The majority of the patients had normal a BMI, level of serum total bilirubin below 10 mg/dL, level of serum albumin above 3 g/dL, elevation of serum liver enzymes as well as abnormal serum tumor markers, CA 19-9 and CEA. Intrahepatic cholangiocarcinoma was the most common site of tumor. Most patients were in an advanced stage, *i.e.*, stage Ⅲ or Ⅳ. One hundred and thirty-three patients received adjuvant chemotherapy of which the combination of fluorouracil and mitomycin C was the most administered regimen (60.9% of these patients). Other regimens included combination of gemcitabine and capecitabine, gemcitabine, fluorouracil, and capecitabine.

Median overall survival of the entire cohort was 17 mo (95%CI: 13.2-20.7) as shown in Figure 1. One, two, and three-year survival rates were 65.5%, 45.2%, and 35.4%. Serum albumin, serum CEA, AJCC staging, pT staging, lymph node metastases and whether or nor having received adjuvant chemotherapy were significant prognostic factors in resectable cholangiocarcinoma by univariate analysis as shown in Table 3. Figure 2 revealed Kaplan-Meier survival curve regarding significant prognostic factors. Receiving adjuvant chemotherapy prolonged survival in resectable cholangiocarcinoma patients, however, the combination between fluorouracil and mitomycin C was not different other regimen to improve survival benefit [median survival time was 17.3 mo (95%CI: 12.8-21.7) *vs* 22.3 mo (95%CI: 20.3-24.3), respectively; $P = 0.20$]. Abnormal serum CEA and lymph node metastasis significantly impacted the overall survival in multivariate analysis (Table 4).

## DISCUSSION

This cohort study had several similar and different characteristics from the previous reports[3,20,21]. Most patients in this study had a BMI below 23; whereas, the majority of patients in the cited previous report were over-

**Table 3 Differences of survival time among significant variable factors when analyzed by univariate analysis**

| Variable | Median survival (mo) | 95%CI | *P* value |
|---|---|---|---|
| Albumin (g/dL) | | | 0.04 |
| < 3 | 12.8 | 7.1-18.4 | |
| ≥ 3 | 19.1 | 14.6-23.5 | |
| CEA (ng/mL) | | | 0.02 |
| < 2.5 | 27.7 | 14.1-41.3 | |
| ≥ 2.5 | 16.5 | 13.0-20.0 | |
| AJCC staging | | | < 0.001 |
| 0 | Not reached | | |
| 1 | Not reached | | |
| 2 | 23.5 | 16.9-30.1 | |
| 3 | 12.8 | 10.6-15.1 | |
| 4 | 12.5 | 9.3-15.7 | |
| Tumor grading | | | 0.01 |
| Well differentiated | 17.9 | 12.6-23.2 | |
| Moderate differentiated | 7.7 | 0.0-21.7 | |
| Margin in resection group | | | 0.001 |
| Negative | 26.7 | 19.6-33.8 | |
| Positive | 14.1 | 11.9-16.4 | |
| pT stage | | | < 0.001 |
| 0 | Not reached | | |
| 1 | 28.6 | 23.1-34.1 | |
| 2 | 19.9 | 12.9-26.9 | |
| 3 | 12.8 | 9.4-16.3 | |
| 4 | 15.5 | 9.9-21.1 | |
| pN stage | | | < 0.001 |
| 0 | 25.1 | 20.0-30.1 | |
| 1 | 10.0 | 6.7-13.3 | |
| Receiving adjuvant chemotherapy | | | 0.01 |
| Yes | 21.6 | 16.9-26.4 | |
| No | 13.4 | 10.7-16.2 | |

CEA: Carcinoembryonic antigen; AJCC: American Joint Committee on Cancer. pN: Pathologic node; pT: Pathologic tumor.

**Table 4 Significant prognostic factors by multivariate analysis**

| Variable | HR | 95%CI | *P* value |
|---|---|---|---|
| Serum CEA (< 2.5 ng/mL *vs* ≥ 2.5 ng/mL) | 1.68 | 1.05-2.66 | 0.027 |
| Lymph node metastasis (yes *vs* no) | 2.27 | 1.24-4.12 | 0.007 |
| Receiving adjuvant chemotherapy (yes *vs* no) | 0.71 | 0.49-1.02 | 0.067 |
| Surgical margin (negative *vs* positive) | 0.72 | 0.49-1.06 | 0.094 |

CEA: Carcinoembryonic antigen; HR: Hazard ratio.

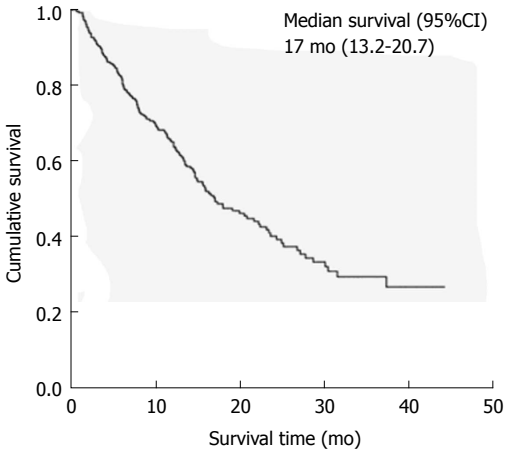


**Figure 1 Kaplan-Meier survival curve used to analyze the overall survival time of 263 resectable cholangiocarcinoma.**

weight[20]. The tumor data showed that intrahepatic cholangiocarcinoma was the most common subtype, whereas, perihilar subtype was the most common location in other reports[3]. These findings were correlated with the first clinical presentation of abdominal pain and level of serum bilirubin below 10 mg/dL. Furthermore, this study found that asymptomatic presentation was more common in patients with intrahepatic cholangiocarcinoma than in other previous studies[21]. The authors' results demonstrated serum albumin was a significant prognostic factor by univariate analysis. Serum albumin is marker of nutritional status in cancer patients[22]. A low level of serum albumin is usually found in malnourished patients, and associated with poor treatment outcomes such as postoperative infection and impaired wound healing[23,24]. Advanced stages of cancers, including cholangiocarcinoma, also lead to a decrease in serum albumin level[25]. Additionally, previous studies reported that low serum albumin was associated with an increased postoperative mortality in cholangiocarcinoma patients[26].

AJCC staging of cholangiocarcinoma, pT staging, and the differentiation of tumor cells were an associated prognostic factor, as well and were demonstrated in our results by univariate analysis. These results were similar with previous results[18,25]. A well-differentiated tumor histology was related to early staging and was a good prognostic factor from results of the previous studies[27,28].

The results showed that the level of serum CEA above 2.5 ng/mL and lymph node metastases were significant independent poor prognostic factors by univariate and multivariate analysis. CEA was demonstrated in fetal gut tissue and in tumors from the gastrointestinal tract[29]. Serum CEA in cancer patients was significantly higher than in healthy controls and may be a prognostic factor in several gastrointestinal cancers, including cholangiocarcinoma[30,31]. A previous study demonstrated that cancer patients with a high level of serum CEA was associated with an advanced stage of cancer and may signal poor prognosis[32,33]. This study demonstrated that cholangiocarcinoma patients with high level of serum CEA were associated high risk of death (HR 1.68, 95%CI: 1.05-2.66), which is similar to previous studies[25]. The preoperative serum CEA level in cholangiocarcinoma patients was correlated with the stage of cancer and could help determine their prognosis[32,34].

Lymphatic dissemination is a common metastatic pathway of cholangiocarcinoma. Previous studies demonstrated that up to 55% of cholangiocarcinoma patients who underwent operations had tumor cells in the regional lymph nodes[9]. Several studies showed that overall survival rate in cholangiocarcinoma patients with lymph node involvement was lower than other groups[35-37]. These findings were similar in both resectable and unresectable patients[25,26,38,39]. The findings of the present

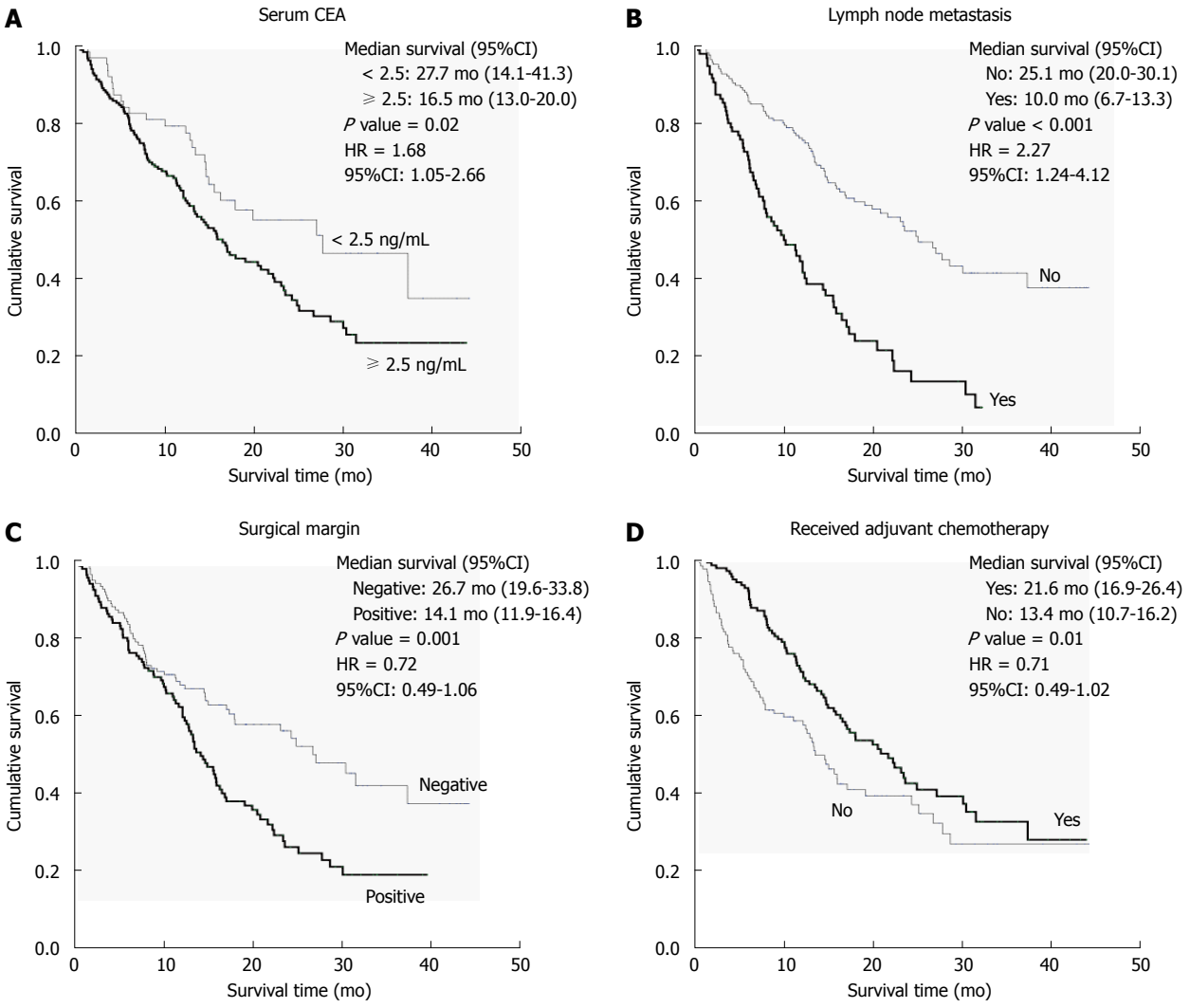


**Figure 2 Kaplan-Meier survival curve showed significant difference in survival rate regarding prognostic factors.** A: Serum carcinoembryonic antigen (CEA) level ⩾ 2.5 ng/mL at presentation; B: Lymph node metastasis; C: Surgical margin; D: Receiving adjuvant chemotherapy. HR: Hazard ratio.

study also showed that lymph node metastases had an impact on survival.

Surgical margin status is a prognostic factor in several cancers, including cholangiocarcinoma. Previous studies showed overall survival rate in cholangiocarcinoma patients with positive surgical margin was lower than patients with negative surgical margin[15,28,40-42]. The present results demonstrated that a negative surgical margin was associated long-term survival time.

Adjuvant chemotherapy is a controversial issue in resectable cholangiocarcinoma. The present authors' results showed that patients with adjuvant chemotherapy may have longer overall survival time than patients without adjuvant chemotherapy. Previous retrospective studies showed benefits of adjuvant chemotherapy[12,15,43]. Randomized studies, however, did not demonstrate a definite advantage in cholangiocarcinoma[44]. Recently, a meta-analysis showed that chemotherapy as a part of adjuvant therapy which included radiotherapy and concurrent chemoradiotherapy may be beneficial in resectable cholangiocarcinoma patients with high risk features, such as lymph node metastases and positive surgical margins[45]. In our institute, combination of 5-fluorouracil and mitomycin C was the most administered regimen. However, the survival of this combination was not significantly different from the other regimens.

In conclusion, serum CEA and lymph node metastasis which are associated with advanced tumor stages become strong negative prognostic factors in cholangiocarcinoma, while additional treatment including adjuvant chemotherapy and adequate surgical resection may improve survival time.

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## COMMENTS

### Background

Cholangiocarcinoma has a high prevalence in the Asian countries, particularly Thailand. Cholangiocarcinoma patients usually have a high mortality rate and poor treatment outcomes. Curative surgery is the only treatment for early stages of this cancer. Cholangiocarcinoma has a high rate of recurrence. This study aimed to evaluate outcomes in resectable cholangiocarcinoma patients and to determine prognostic factors.

### Research frontiers

A retrospective study included newly-diagnosed 263 cholangiocarcinoma patients from January 2009 to December 2011 who underwent curative resection and had pathological reports with clear margins or microscopic margins in Srinakarind Hospital (a 1000-bed university hospital).

### Innovations and breakthroughs

The results demonstrated serum carcinoembryonic antigen and lymph node metastases which were associated with advanced stage tumors become strong negative prognostic factors in cholangiocarcinoma, while additional treatment including adjuvant chemotherapy and adequate surgical resection may improve survival time.

### Applications

Adjuvant chemotherapy and adequate surgical resection may improve survival time.

### Terminology

Curative resection was defined as a total excision of the entire tumor, including the primary tumor and the associated lymph node drainage fields.

### Peer review

This is an interesting study aimed to evaluate outcomes in resectable cholangiocarcinoma patients and to determine prognostic factors. The results are interesting and suggest that adjuvant chemotherapy which includes combination of fluorouracil and mitomycin C and other regimens may improve overall survival in resectable cholangiocarcinoma patients.

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1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

*Chinese journal article (list all authors and include the PMID where applicable)*

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

*In press*

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

*Organization as author*

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 DOI:10.1161/01.HYP.0000035706.28494.09]

*Both personal authors and an organization as author*

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

*No author given*

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

*Volume with supplement*

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

*Issue with no volume*

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

*No volume or issue*

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

**Books**

*Personal author(s)*

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

*Chapter in a book (list all authors)*

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

*Author(s) and editor(s)*

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

*Conference proceedings*

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

*Conference paper*

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

**Electronic journal** (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

**Patent** (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Write as mean ± SD or mean ± SE.

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Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as $\chi^2$ (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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