sampling proposed by Copas and Li (1997). Here, we briefly review their approach.

Suppose that when conducting a meta-analysis, there is a hypothetical population of studies which consists of all the studies, published or unpublished, in the research area of interest, and only a part of it is published and identified through a systematic literature search. A random effects model is assumed to this population

$$y_i = \mu_i + \sigma_i \varepsilon_i, \quad \varepsilon_i \sim \mathrm{N}(0,1), \quad \mu_i \sim \mathrm{N}(\mu, \tau^2), \quad i = 1, \cdots, n, \tag{1}$$

where $y_i$ is the estimated effect of interest in the study $i$, $\mu$ is the overall mean effect, $\tau^2$ is the heterogeneity variance, $\sigma_i^2$ is the within-study sampling variance, $n$ is total number of studies, and $\varepsilon_i$ and $\mu_i$ are assumed to be independent.

Selectivity is modeled using a separate selection equation with a single correlation

$$z_i = \gamma_0 + \frac{\gamma_1}{s_i} + \delta_i, \quad \delta_i \sim \mathrm{N}(0,1), \quad \mathrm{corr}(\varepsilon_i, \delta_i) = \rho, \tag{2}$$

where $z_i$ is a latent variable which is used in defining the selection process, $s_i$ is a reported within-study standard error, $\gamma_0$ and $\gamma_1$ are sensitivity parameters controlling the marginal probability of a study with a standard error $s_i$ being selected — $\gamma_0$ controls the overall publication probability and $\gamma_1$ controls how the publication probability depends on $s_i$ — and the residuals $(\varepsilon_i, \delta_i)$ are assumed to be jointly normal. The role of equation (2) is that $y_i$ *is observed (selected for meta-analysis) only when the latent variable* $z_i > 0$, thus defining a probit-type selectivity with censoring which is common in econometrics literature (Maddala, 1983). $y_i$ and $s_i$ are assumed to be independent, so that when $\rho = 0$ this model describes a situation in which no publication bias exists. When $\rho > 0$, selected studies with positive $z_i$ tend to have more positive $\delta_i$, hence more positive $\varepsilon_i$, which leads to a positive bias in $y_i$. The conditional expectation of $y_i$ including a bias term can be shown explicitly as

$$\mathrm{E}(y_i | z_i > 0, s_i) = \mu + \rho \sigma_i \lambda\left(\gamma_0 + \frac{\gamma_1}{s_i}\right), \tag{3}$$

where $\lambda(\cdot)$ is Mill's ratio $\phi(\cdot)/\Phi(\cdot)$, $\phi$ and $\Phi$ describing the density and distribution functions, respectively, of the standard normal distribution.

As the distribution of $y_i$ in a selected study is given by the conditional distribution of $y_i$ given that $z_i > 0$, the likelihood function can be written down as

$$\begin{aligned} L(\mu, \rho, \tau, \sigma, \gamma_0, \gamma_1) &= \sum_{i=1}^{m} [\log p(y_i | z_i > 0, s_i)] \\ &= \sum_{i=1}^{m} \left[ -\frac{1}{2} \log(\tau^2 + \sigma_i^2) - \frac{(y_i - \mu)^2}{2(\tau^2 + \sigma_i^2)} + \log \Phi(v_i) - \log \Phi(u_i) \right], \end{aligned} \tag{4}$$

where $m$ is the number of the selected studies, and

$$u_i = \gamma_0 + \frac{\gamma_1}{s_i}$$

$$v_i = u_i + \widetilde{\rho}_i \frac{y_i - \mu}{\sqrt{\tau^2 + \sigma_i^2}} \Big/ \sqrt{1 - \widetilde{\rho}^2}$$

$$\widetilde{\rho} = \frac{\sigma_i}{\sqrt{\tau^2 + \sigma_i^2}} \rho.$$

Assuming that each study has a sufficiently large sample size, the nuisance parameter $\sigma_i^2$ can be replaced by their estimates based on $s_i^2$,

$$\widehat{\sigma_i^2} = \frac{s_i^2}{1 - \lambda(u_i)(u_i + \lambda(u_i))\rho^2},$$

using the fact that $s_i^2$ is an estimated conditional variance $\mathrm{Var}(\sigma_i^2 | z_i > 0)$.

### 2.2 Sensitivity analysis for publication bias

Copas and Shi (2000a) used the likelihood function (4) to find the profile likelihood for the sensitivity parameters $(\gamma_0, \gamma_1)$ and showed that this likelihood has a very flat plateau, suggesting that the available information is not enough to estimate the values of these parameters. Instead, they proposed a sensitivity analysis approach — they obtained maximum likelihood estimates of $(\mu, \rho, \tau)$ under given sensitivity parameters $(\gamma_0, \gamma_1)$ by numerical optimization, and examined the sensitivity of the estimated value of the parameter of main interest $\mu$ to various combinations of sensitivity parameter values.

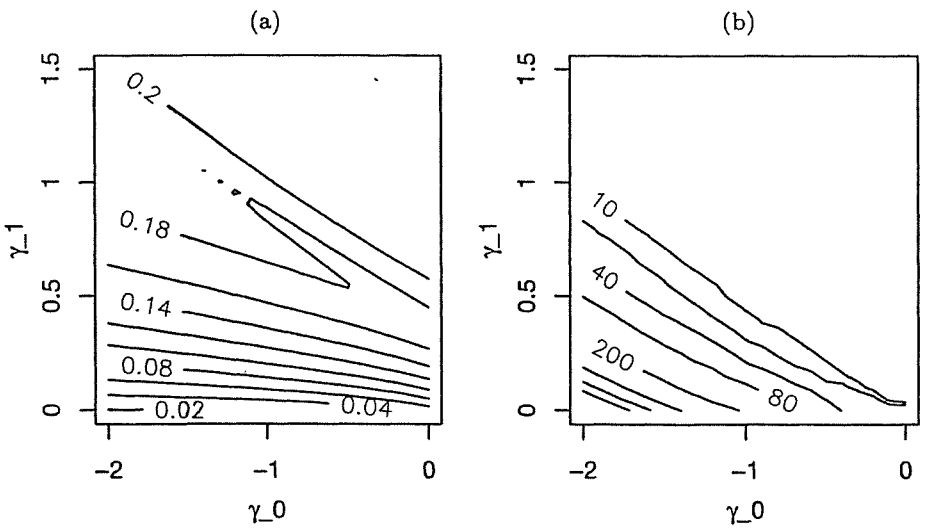


**Fig. 1.** Contour plots of (a) $\mu$, and (b) number of unpublished studies, under the various values of sensitivity parameters using passive smoking and lung cancer data (Hackshaw et al., 1997).

Figure 1 (a) shows a contour plot of $\widehat{\mu}$, the maximum likelihood estimate of $\mu$, under various values of sensitivity parameters. The data used is from the passive smoking meta-analysis based on 37 studies and $\mu$ stands for the population mean of the log-relative risk. When no unpublished study is assumed (upper right) $\widehat{\mu}$ is 0.217, consistent with the estimate from the usual random-effects meta-analysis (DerSimonian and Laird, 1986). On the other hand, with more and more

unpublished studies being assumed (lower left), overestimation of $\widehat{\mu}$ due to publication bias is corrected and it approaches, and finally almost equals to, zero.

In this figure the ranges of sensitivity parameters are set to $[-2,0]$ for $\gamma_0$ and $[0,1.5]$ for $\gamma_1$, respectively. In order to assess the appropriateness of these settings, these parameters are transformed into a more intuitive measure, the estimated number of unpublished studies (NUPS),

$$\sum_{i=1}^{m}\left\{\Phi\left(\gamma_0+\frac{\gamma_1}{s_i}\right)\right\}^{-1}-m, \tag{5}$$

assuming that, if a study with a publication probability of $p$ is published and selected for meta-analysis, there is supposedly $p^{-1}-1$ equivalent studies remaining unpublished (Copas and Shi, 2001). Figure 1 (b) shows the distribution of NUPS. The sensitivity parameters in these ranges correspond to NUPS from zero (upper right) to $>1000$ (lower left), which seems wide enough to cover the plausible range of inference.

But here remains another problem — these ranges may seem to some *too wide*. In fact, Copas and Shi (2000b) adopted much more modest assumptions about the sizes of NUPS, as we will see in Section 3, in the non-technical article on passive smoking meta-analysis. Yet they were criticized by some of the environmental health experts for assuming unrealistically large NUPS (Hackshaw et al., 2000). What is needed is to provide a realistic basis for determining the appropriate ranges of the sensitivity parameters, and as a solution for this we propose a Bayesian approach incorporating the prior belief expressed by the experts as a prior distribution of NUPS.

### 2.3 Prior distributions

We assume a normal prior distribution for the sensitivity parameter $\gamma_0$,

$$\gamma_0 \sim \mathrm{N}(\mu_\gamma, \sigma_\gamma^2), \tag{6}$$

and fix another sensitivity parameter $\gamma_1$ at $\frac{3}{4}\gamma_0+\frac{3}{2}$, i.e. $(\gamma_0,\gamma_1)$ is only allowed to move along the upward diagonal of the Figure 1 (a) and (b). This restriction is largely for computational ease, and should not influence substantially on the sensitivity of $\widehat{\mu}$ to the sensitivity parameters as the contours in Figure 1 (a) and (b) are roughly parallel (Copas, 1999). The value of $\gamma_0$ does not allow a direct clinical interpretation, and we transform this distribution to that of NUPS using formula (5), according to which we select the hyperparameters for $\gamma_0$ as we discuss in detail in §3.2.

We assume noninformative prior distributions for the other parameters; a normal distribution with mean 0 and variance $10^6$ for $\mu$, a uniform distribution in $[0,1]$ for $\rho$, and $\tau^2 \sim 1/\tau^2$.

### 2.4 Posterior distribution and sampling procedure

Letting $L(\mu,\rho,\tau,\gamma_0)$ denote the log-likelihood given by equation (4), in which nuisance parameter $\sigma$ is eliminated and $\gamma_1$ is fixed, and $\{\cdot\}$ denote marginal distributions, the joint posterior distribution of all unknown model parameters is expressed as

$$\exp L(\mu,\rho,\tau,\gamma_0)\times\{\mu\}\{\rho\}\{\tau^2\}\{\gamma_0\}, \tag{7}$$

assuming all the prior distributions are independent. It can be estimated using the Gibbs sampling, a class of Markov Chain Monte Carlo scheme where the transition kernel is formed by the full conditional distributions. The full conditional distribution of each unknown parameter is formed by conditioning the joint posterior distribution on the data and on the current values of all the other parameters. Letting $D$ denote data and $\{\cdot|\cdot\}$ denote conditional distributions, we have the following:

$$\begin{aligned}
\{\mu|D,\rho,\tau^2,\gamma_0\} &\propto \exp L(\mu,\rho,\tau,\gamma_0)\times\{\mu\}\\
\{\rho|D,\mu,\tau^2,\gamma_0\} &\propto \exp L(\mu,\rho,\tau,\gamma_0)\times\{\rho\}\\
\{\tau^2|D,\mu,\rho,\gamma_0\} &\propto \exp L(\mu,\rho,\tau,\gamma_0)\times\{\tau^2\}\\
\{\gamma_0|D,\mu,\rho,\tau^2\} &\propto \exp L(\mu,\rho,\tau,\gamma_0)\times\{\gamma_0\}.
\end{aligned}$$

In some cases, the full conditional distributions used in the Gibbs sampling can be reduced analytically to the well-known distributions for which methods for efficient random sampling is available. However, such reduction is not possible for this case due to the non-linearity of the likelihood, and we have to perform a direct univariate sampling from each full conditional distribution. For this purpose we use the adaptive rejection Metropolis sampling (ARMS) algorithm (Gilks et al., 1995), a generalization of the adaptive rejection sampling (ARS) algorithm (Gilks and Wild, 1992). ARS is an algorithm for generating random samples from a log-concave target distribution by rejection sampling using a piecewise exponential proposal distribution and updating it repeatedly. ARMS generalizes ARS by introducing the Metropolis step and accommodating non-log-concavity of the target distribution. For further details of these algorithms, see the references.

The code for Gibbs sampling used in this article was written in R-2.1.1 (R Development Core Team, 2005). For the adaptive rejection Metropolis sampling, the original code written in C and FORTRAN by W. R. Gilks, and its wrapper code for R written in G. Petris and L. Tardella are both available online.

## 3. Application

### 3.1 Reanalysis of passive smoking and lung cancer meta-analysis

In a meta-analysis of epidemiological studies investigating the relationship between passive smoking and lung cancer, Hackshaw et al. (1997) identified 37 observational studies for the risk of lung cancer in female non-smokers who lived or did not live with a smoker. Figure 2 shows the funnel plot of these 37 studies, plotting the standard error $s_i$ against the log-relative risk $y_i$. The dotted line in the figure indicates the overall log-relative risk, 0.217 (95% confidence interval 0.122 - 0.306), estimated using a random-effects model (DerSimonian and Laird, 1986). We see a clear tendency for the smaller studies with larger standard errors to give more positive results than the larger studies, suggesting the influence of publication bias.

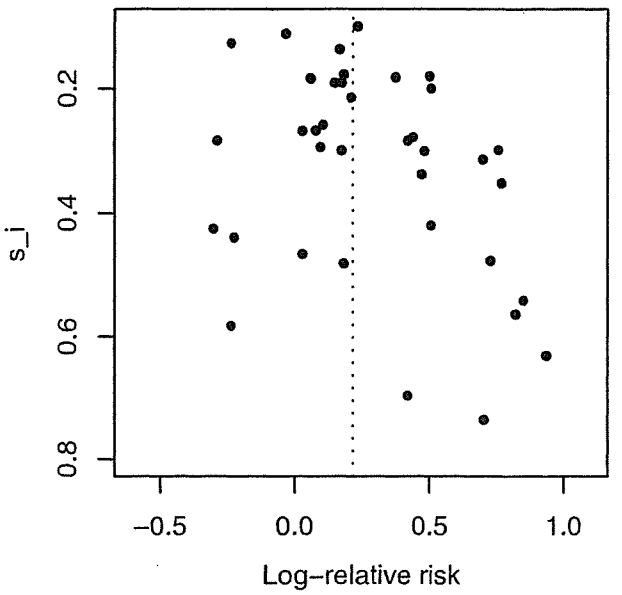


**Fig. 2.** Funnel plot for the passive smoking meta-analysis (Hackshaw et al., 1997). Dotted line indicates the estimated overall log-relative risk, 0.217.

Copas and Shi (2000b) conducted a reanalysis of these data with the model described in Section 2 examining the sensitivity of the parameter estimation to publication bias. They assumed five different levels of NUPS, (0, 11, 23, 38, 60), corresponding to five different *canonical probabilities* of (1, 0.9, 0.8, 0.7, 0.6) which approximate (but not equal to) the publication probabilities within the population of published and unpublished studies (Copas and Shi, 2000a). The overall mean of log-relative risk was estimated as (0.217, 0.166, 0.140, 0.122, 0.104), respectively, and they concluded that at least some publication bias is needed to explain the trend seen in the funnel plot and that even a modest degree of publication bias leads to a substantial reduction in the relative risk.

Later several critical comments were submitted by the experts in this research area. Hackshaw et al. (2000) stated that what Copas had made is an "extreme assumption that 40% of studies were not published", far from being modest. They also emphasized that the range of the relative risk estimated by the Copas's sensitivity analysis, 0.104 - 0.217, is in large part covered with the 95% confidence interval of the overall relative risk shown in the original meta-analysis, 0.122 - 0.307, so the impact is not so serious. Glantz (2000) argued that their own empirical data (Bero et al., 1994) suggest that the size of NUPS in this area is very small and it is unlikely that there is so many unpublished studies as Copas assumed.

### 3.2 Sensitivity analysis incorporating the experts' prior beliefs

In order to elicit the hyperparameters $(\mu_\gamma, \sigma_\gamma^2)$, we first transform the normal prior distributions of $\gamma_0$ into the directly interpretable distributions of NUPS, based on which we select the appropriate hyperparameters of $\gamma_0$ for the sensitivity analysis. Figure 3 (a) shows the selected

three prior distributions of $\gamma_0$, and Figure 3 (b) shows the corresponding distributions of NUPS. Since the prior distributions of NUPS shown in Figure 3 (b) are not well-known parametric distributions, we conducted a grid-search of the hyperparameters $(\mu_\gamma, \sigma_\gamma^2)$ to select the distributions with appropriate credible intervals.

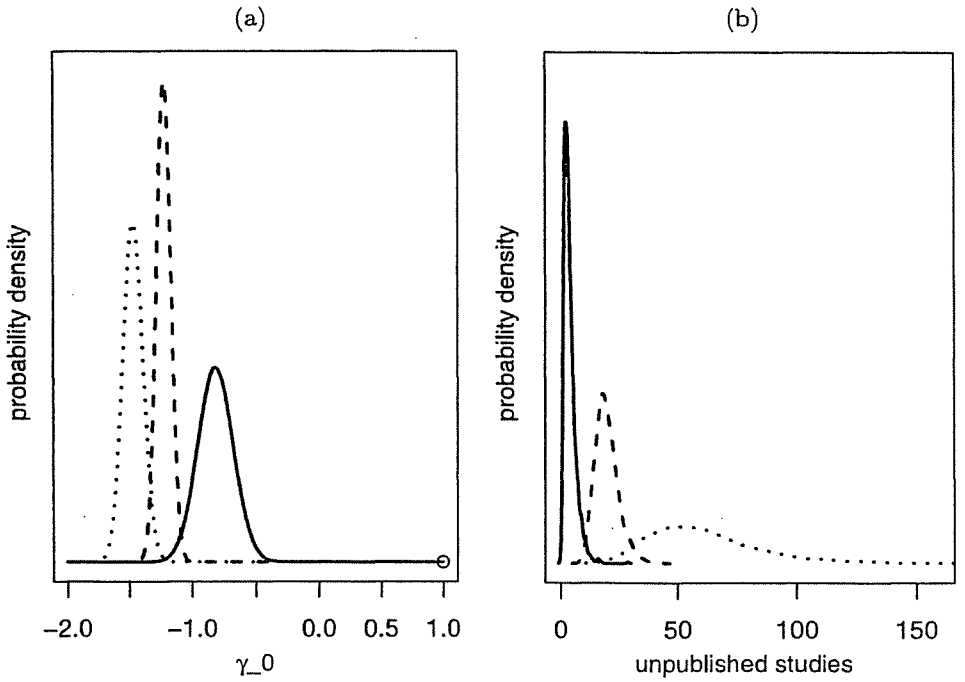


**Fig. 3.** Prior distributions of the sensitivity parameter $\gamma_0$ and the number of unpublished studies. Solid line; prior 1. Broken line; prior 2. Dotted line; prior 3.

In Figure 3 (b), Prior 1 (solid line, mode 3 and a 90% interval [1, 9]) represents the prior belief that the size of NUPS is very small (< 10), corresponding to the experts' opinion based on their empirical data. Prior 2 (dashed line, mode 19 and a 90% interval [12, 29]) represents the "extreme" prior that the unpublished proportion of the population is around 40%, corresponding to the assumption in Copas's sensitivity analysis which was regarded as "extreme assumption" by an expert. And prior 3 (dotted line, mode 58 and a 90% interval [31, 112]), added for the purpose of sensitivity analysis, represents an even more extreme prior than what is regarded as extreme by the experts.

For the posterior simulation we ran each chain of Gibbs sampling described in Section 2 for 10,000 iterations and discarded the first 5,000 iterations. The convergence of chains was assessed using the method of Gelman and Rubin (1992).

### 3.3 Results

Table 1 shows the summary of the posterior estimates under different prior distributions of sensitivity parameter $\gamma_0$, with the marginal posterior distribution for $\mu$ also shown in Figure 4.

The estimated values of the parameter of interest, $\mu$, can be interpreted as follows. Under

**Table 1.** Summary of the result of the Gibbs sampling.

| | Prior 1 | | | Prior 2 | | | Prior 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | 95% HPD | Mean | SD | 95% HPD | Mean | SD | 95% HPD |
| $\mu$ | 0.196 | 0.0501 | (0.0954, 0.298) | 0.167 | 0.0511 | (0.0668, 0.266) | 0.137 | 0.0582 | (0.0243, 0.254) |
| $\rho$ | 0.573 | 0.276 | (0.0842, 0.999) | 0.480 | 0.212 | (0.0642, 0.851) | 0.407 | 0.172 | (0.0227, 0.681) |
| $\tau^2$ | 0.0174 | 0.0185 | (0.0001, 0.0491) | 0.0148 | 0.0165 | (0.0001, 0.0438) | 0.0129 | 0.0155 | (0.0001, 0.040) |
| $\gamma_0$ | −0.828 | 0.140 | (−1.107, −0.560) | −1.225 | 0.0571 | (−1.336, −1.113) | −1.467 | 0.0810 | (−1.626, −1.312) |

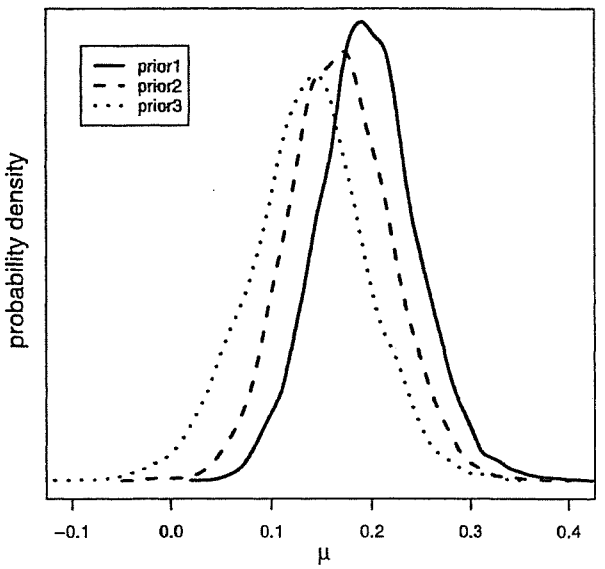


**Fig. 4.** Marginal posterior distribution for $\mu$.

the prior 1, which reflects the belief that the size of NUPS is very small, the posterior mode of $\mu$ is estimated as 0.194 and the influence of publication bias seems to be only modest. Under the prior 2 the posterior mode of $\mu$ is 0.167, and even this prior represents an extreme opinion from the experts' point of view, the 95% Highest Probability Density (HPD) interval of the mariginal posterior of $\mu$ is mostly within the 95% interval of the original meta-analysis, suggesting that the result from the original meta-analysis is robust against the publication bias. Moreover, even under the prior 3, the most extreme and far exceeding the plausible range of the experts' view, the posterior mode of $\mu$ is 0.134 and its 95% HPD interval does not include zero, thus adding more strength to the conclusion of the original meta-analysis.

## 4. Discussion

One of the practical difficulties in performing sensitivity analysis for publication bias is the determination of an appropriate range of sensitivity parameters. In many cases it is not possible to narrow down the range because no objective data regarding the magnitude of publication bias is available, while setting too wide a range may lead us to underestimate, or fail to detect, the true effect. As a solution for this issue we proposed in this article the way to incorporate the

experts' subjective opinions in the analysis. Experts often bear a rough estimate of the amount of unpublished literature in their research area, which can be utilized for the elicitation of the prior distribution of sensitivity parameters. These prior distributions are introduced into the Copas's model, making the problem of determining the range of sensitivity parameters reduced to that of sensitivity analysis of various prior distributions in a formal Bayesian inference.

Among the researchers studying the association between passive smoking and lung cancer, the influence of publication bias on the risk estimate has been a sensitive issue and discussed extensively since 1990s. One reason for this is the long continuing debate between researchers and the tobacco industry. Researchers had to argue against the industry which contended that the positive conclusions of passive smoking meta-analysis is exaggerated due to publication bias. They executed extensive literature searches for unpublished studies such as dissertations and proceedings of symposia, including tobacco industory-affiliated ones (Bero et al., 1994), which forms the background for the experts' comments cited in §3.1.

In this article we employed for simplicity the wordings of experts' comments on published papers as the basis for the prior elicitation, but if we are allowed to contact some of the experts, direct elicitation with more careful and sophisticated methodology is also possible (Spiegelhalter et al., 2004). In this situation, the flexibility of the Bayesian framework we proposed in this article, which accommodates any prior distributions, offers more advantages since we do not know in advance to what family of distribution the elicited prior belongs. Copas's sensitivity analysis will approximate the result of proposed method if the elicited prior distribution of $\gamma_0$ is unimodal and symmetric.

The assumption of independence between $y_i$ and $s_i$ is a minor but essential problem in Copas's model for publication bias, because some authors suggest there are cases where this assumption does not hold (Sterne et al., 2001). For example, small studies with large standard errors tend to report overestimated outcomes because of the lack of rigorous methodology, or studies with many high-risk subjects reporting highly positive outcomes tend to be small because of the difficulty in accruing such subjects. Although the assumption of independence is unverifiable from the data, the sensitivity analysis assuming some fixed values of the correlation between $y_i$ and $s_i$ may be useful. For this issue, further research will be needed.

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# Uracil-Tegafur as an Adjuvant for Hepatocellular Carcinoma: A Randomized Trial

Kiyoshi Hasegawa,[1] Tadatoshi Takayama,[2] Masayoshi Ijichi,[1] Yutaka Matsuyama,[3] Hiroshi Imamura,[1] Keiji Sano,[1] Yasuhiko Sugawara,[1] Norihiro Kokudo,[1] and Masatoshi Makuuchi[1]

**Frequent recurrence of hepatocellular carcinoma (HCC) after surgery remains a major clinical problem. This randomized controlled trial evaluated whether postoperative adjuvant therapy with oral uracil-tegafur (UFT) prevents recurrence of HCC. A total of 160 patients who underwent curative hepatic resection for HCC were randomly assigned to receive either 300 mg/day of UFT for 1 year after surgery (n = 79, UFT group) or surgery alone (n = 80, control group). The primary endpoint was recurrence-free survival, and the secondary endpoint was overall survival. Other study variables included liver function and type of recurrence. During a median follow-up of 4.8 years (range: 0.5-7.9), recurrence-free survival curves in the groups were similar ($P$ = .87). Overall survival was slightly but not significantly worse in the UFT group than in the control group ($P$ = .08). The rates of recurrence-free and overall survival at 5 years were 29% and 58%, respectively, in the UFT group, as compared with 29% and 73%, respectively, in the control group. The hazard ratio for recurrence in the UFT group, relative to the control, was 1.01 (95% confidence interval: 0.84-1.22, $P$ = .87). The proportion of patients with advanced recurrence (i.e., multiple, extrahepatic, or associated with vascular invasion) was significantly higher in the UFT group (74%, 43 of 58 patients with recurrence) than in the control group (53%, 30 of 57) ($P$ = .02). In conclusion, our results offer no evidence to support potential benefits of adjuvant chemotherapy with UFT after surgery in patients with HCC and suggest that such treatment may even worsen overall survival.** (HEPATOLOGY 2006;44:891-895.)

Hepatic resection has been established as one of the most effective and safe therapeutic options for hepatocellular carcinoma (HCC).[1,2] However, frequent recurrence of HCC even after curative surgery remains a major clinical problem.[3] Several adjuvant treatments have been used to prevent recurrence after surgery, but their effectiveness remains controversial.[4-7] Uracil-tegafur (UFT, Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) combines tegafur, a prodrug of 5-fluorouracil, with uracil, a biochemical modulator, in a molar ratio of 4:1. UFT has been reported to be effective against colorectal[8] and lung adenocarcinomas,[9] as well as HCC.[10,11] We tested the hypothesis that adjuvant chemotherapy with UFT can prevent disease recurrence after hepatic resection in patients with HCC. Because UFT is administered orally, we considered that this treatment would be clinically useful if its effectiveness could be confirmed.

## Patients and Methods

***Eligibility Criteria.*** Patients with HCC who had undergone their first curative hepatic resection at Tokyo University Hospital were eligible for this trial if they met the following entry criteria: cirrhosis of Child-Pugh class A or B; adequate bone marrow and renal functions (white blood cell count $>4.0 \times 10^3/\mu L$, platelet count $>50 \times 10^3/\mu L$, and serum creatinine level $<1.5$ mg/dL); and an age between 15 and 79 years. The exclusion criteria were the presence of clinically confirmed extrahepatic metastasis, macroscopic evidence of tumor thrombus in the infe-

*Abbreviations: ALT, alanine aminotransferase, HCC, hepatocellular carcinoma; UFT, uracil-tegafur.*

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*Clinical trial registration No. C000000445.*

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rior vena cava or the main portal vein, other previous or synchronous malignant disorders, and postoperative dysfunction of any organ.

***Study Design.*** The protocol for this trial was approved by the local ethical committee. The English summary of the protocol has been disclosed (registration number: C000000445) in the Clinical Trials Registry managed by the University Hospital Medical Information Network in Japan, which can be accessed free on the internet (www.umin.ac.jp/ctr/index.htm).The protocol was explained to eligible patients, and informed consent was obtained from all subjects before enrollment. Enrolled patients were stratified according to age (15-59 years vs. 60-79 years), the indocyanine green retention rate at 15 minutes (<20% vs. ≥20%), and the presence or absence of macroscopically evident vascular invasion. Patients were randomly assigned to either the UFT group or the control group by the minimization technique.[12] We created the minimization program using Microsoft Excel (for Windows) and Visual Basic. A single investigator (K.H.) not involved in surgery or patient follow-up was responsible for patient allocation and enrollment, group assignment, and informing other investigators of the assigned treatment. Because a placebo was unavailable, the study was not blinded.

The UFT group received oral UFT (300 mg/day) for 1 year after surgery. The lower limit of the recommended dose was used to avoid drug-induced liver dysfunction, taking into account the severely compromised liver function of the patients at study entry. The control group received surgery alone. During the trial period, no patient received other anticancer drugs or any antiviral therapy to treat hepatitis. After surgery, patients in both groups underwent ultrasonography and measurement of tumor markers (α-fetoprotein and des-γ-carboxy prothrombin) every 2 months, dynamic computed tomography every 4 months, and chest radiography every 6 months, as had been done in a previous study.[6] If intrahepatic recurrence was suspected, hepatic angiography followed by Lipiodol computed tomography was performed. Recurrence was defined as lesions with typical findings of HCC on two or more imaging methods. In patients who had recurrence or the development of another malignant disorder, treatment with UFT was withdrawn. Patients with local recurrence in the liver underwent a second hepatic resection, if the functional reserve of the liver permitted operation and curative surgery was possible. Other patients received local ablation, systematic chemotherapy, or transcatheter hepatic arterial chemoembolization, if possible.

The primary endpoint was recurrence-free survival, and the secondary endpoint was overall survival. Other study variables included recurrence type and liver function (serum albumin, alanine aminotransferase [ALT], and total bilirubin levels), evaluated 1 year after surgery or before further treatment in patients who had recurrence within 1 year.

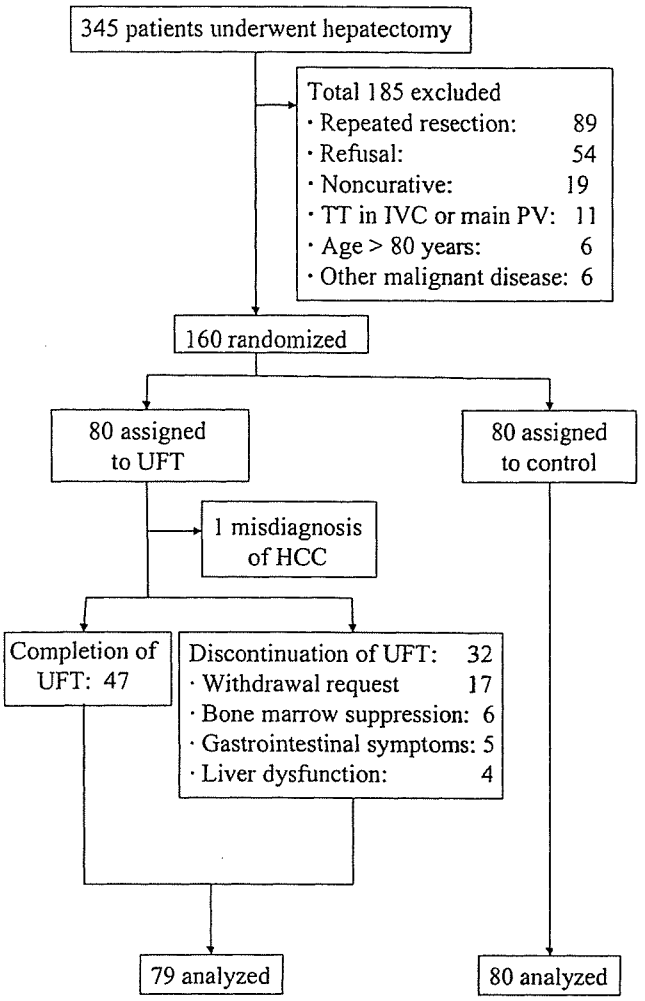


Fig. 1. The trial profile. TT, tumor thrombus; IVC, inferior vena cava; PV, portal vein; UFT, uracil-tegafur; HCC, hepatocellular carcinoma.

***Statistical Analysis.*** All analyses were performed on an intention-to-treat basis. The Wilcoxon rank-sum test and Fisher's exact test were used for comparisons of continuous and the categorical data, respectively. All continuous data are expressed as medians with ranges. Recurrence-free and overall survival curves were estimated by the Kaplan-Meier method, and survival rates were compared between the groups by the log-rank test. The effect of treatment with UFT on recurrence-free survival was estimated using a Cox's proportional-hazards model with no other covariate. The results of this analysis are expressed as hazard ratios with 95% confidence intervals. Statistical significance was defined as a $P$ value less than .05.

We hypothesized that treatment with UFT would increase the rate of recurrence-free survival at 3 years from

**Table 1. Baseline Characteristics**

| Variables | UFT (n = 79) | Control (n = 80) | P |
|---|---|---|---|
| Age (yr)* | 65 (29-75) | 64 (35-78) | .93 |
| Gender (male/female) | 60/19 | 65/15 | .41 |
| Child-Pugh class (A/B) | 68/11 | 70/10 | .82 |
| ICG R15 (%)*,** | 15 (2-44) | 15 (5-40) | .40 |
| Hepatitis (HBV/HCV/none) | 14/58/7 | 15/56/9 | - |
| Background liver (cirrhosis/noncirrhosis) | 42/37 | 38/42 | .53 |
| Serum albumin before surgery (g/dL)* | 3.5 (2.3-4.5) | 3.7 (2.7-4.4) | .11 |
| Serum ALT before surgery (IU/L)* | 51 (9-291) | 47 (8-174) | .45 |
| Serum total bilirubin before surgery (mg/dL)* | 0.8 (0.4-1.5) | 0.8 (0.3-1.8) | .95 |
| Tumor number (single/multiple) | 53/26 | 58/22 | .50 |
| Tumor size (mm)* | 33 (12-120) | 34 (7-130) | .65 |
| Vascular invasion (yes/no) | 18/61 | 17/63 | .85 |
| Alpha-fetoprotein (ng/mL)* | 29 (2-49715) | 29 (1-49388) | .47 |
| Hepatectomy procedure (major/minor) | 16/63 | 20/60 | .57 |
| Blood loss (mL)* | 480 (15-2957) | 615 (70-4830) | .39 |
| Hospital stay (days)* | 17 (9-48) | 18 (9-41) | .41 |
| Mortality | 0 (0%) | 0 (0%) | - |

*Median with range.
**ICG R15, indocyanine green retention rate at 15 min.

30%[6] to 50%, and that 146 patients would be required to detect a significant difference with a 1-tailed type I error of 5% and a statistical power of 80%. Assuming a 10% dropout rate, we set a goal of 160 patients for this trial. Interim analysis was not scheduled. Calculations were performed with JMP 5.1 computer software (SAS Institute Inc., Cary, NC).

***Role of Funding Sources.*** The sponsors of this study had no role in study design; in the collection, analysis, or interpretation of the data; in writing the report; or in the decision to submit the paper for publication.

## Results

From 1997 through 2002, 345 patients underwent a first curative liver resection for HCC at Tokyo University Hospital. A total of 185 patients were excluded for the reasons shown in Fig. 1. The remaining 160 patients were randomly assigned to either the UFT group (n = 80) or the control (n = 80) group. One patient assigned to the UFT group was found to be ineligible after enrollment because HCC had been misdiagnosed. Data from the other 159 patients were analyzed. The baseline characteristics of the two groups were similar (Table 1). Treatment with UFT was temporarily or permanently discontinued in 32 patients (41%) because of bone marrow suppression (n = 6), withdrawal of consent (n = 17), nausea (n = 3), diarrhea (n = 2), and liver dysfunction (n = 4). All adverse events responded to conservative therapy.

Median follow-up was 4.8 years (range: 0.5-7.9). Only one patient in the UFT group was lost to follow up. Recurrence-free survival ($P = .87$) and overall survival ($P = .08$) were similar in the groups (Fig. 2). The rates of recurrence-free survival at 3 and 5 years were respectively 41% and 29% in the UFT group, as compared with 37% and 29% in the control group. The rates of overall survival at 3 and 5 years were respectively 90%, and 58% in the UFT group, as compared with 92% and 73% in the

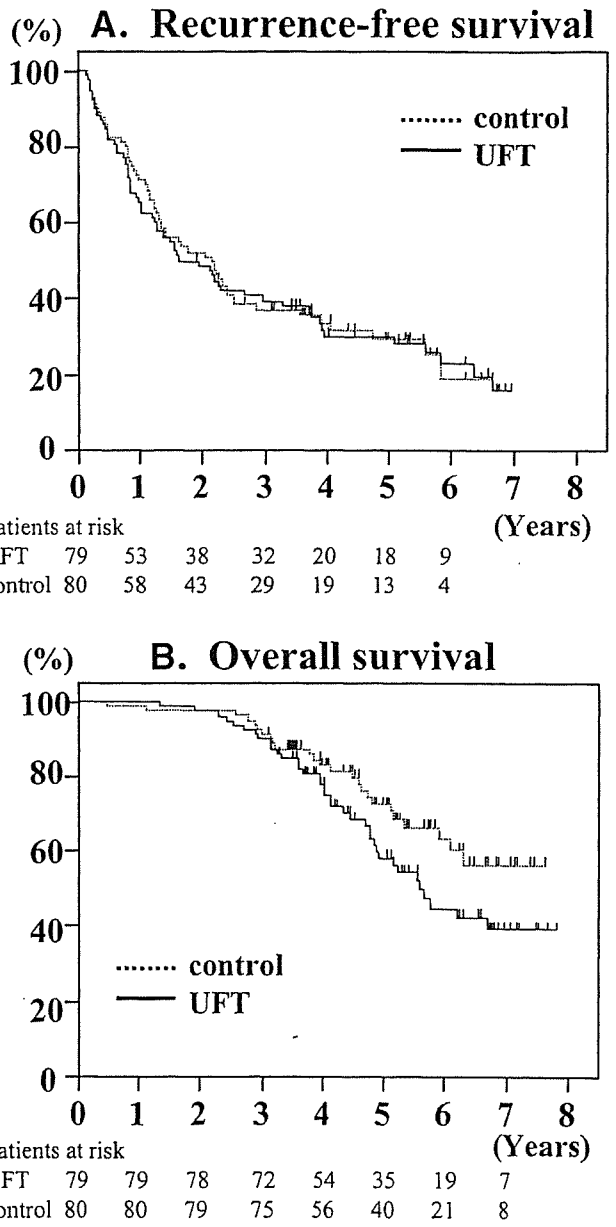


Fig. 2. (A) Recurrence-free survival curves of the UFT (line) and the control (dotted line) groups. Five-year recurrence-free rates were similar (29% vs. 29%, $P = .87$) between the two groups. (B) Overall survival curves of the 2 groups. Five-year overall survival rate of the UFT group was slightly lower than that of the control group (58% vs. 73%, $P = .08$), although the difference was not statistically significant.

control group. The hazard ratio for recurrence in the UFT group, relative to the control, was 1.01 (95% confidence interval: 0.84-1.22, $P = .87$).

Recurrence was advanced (*i.e.*, multiple, extrahepatic, or associated with vascular invasion) in 43 of the 58 patients (74%) with recurrence in the UFT group, as compared with 30 of the 57 (53%) patients with recurrence in the control group (Table 2). The proportion of patients with advanced recurrence was significantly higher in the UFT group than in the control group ($P = .02$). Liver function after surgery, assessed on the basis of serum albumin, alanine aminotransferase, and total bilirubin levels, did not differ significantly between the groups (Table 3).

## Discussion

In this study, recurrence-free survival curves were nearly identical in the UFT group and control group. This trial provided no evidence that treatment with oral UFT prevented postoperative recurrence of HCC after hepatic resection, as compared with surgery alone.

Theoretically, HCC recurs through metastasis from a primary tumor or the development of a second primary tumor in an injured liver.[3] Transcatheter arterial chemoembolization with $^{131}$I-labeled iodized oil[5] and adoptive immunotherapy[6] have been reported to be effective for the prevention of metastasis. However, these adjuvant therapies are extremely expensive and require special equipment and techniques to prepare and dispose of the isotope labeling material[5] or to purify and culture the patient-related lymphocytes.[6] Retinoids[4] and interferon[7] have also been used as adjuvant therapy to prevent the development of second primary tumors, but the value of these treatments is not widely accepted, in spite of the recent promising result.[13] Adjuvant therapy that can prevent the recurrence of HCC after curative resection thus remains to be established. Because UFT has been reported to be effective against HCC,[10,11] we expected that it would prevent metastatic recurrence caused by HCC cells present in the microcirculation. However, the results of our study were negative.

**Table 2. Postoperative Recurrence**

| Variables | UFT (n = 79) | Control (n = 80) | P |
|---|---|---|---|
| Recurrence | | | .86 |
| No | 21 | 23 | |
| Yes | 58 | 57 | |
| Recurrence type | | | .02 |
| Advanced* | 43 (74%) | 30 (53%) | |
| Less advanced† | 15 (26%) | 27 (47%) | |
| Treatment for primary recurrence | | | .08 |
| Surgical | 16 (28%) | 25 (44%) | |
| Nonsurgical | 42 (72%) | 32 (56%) | |

*Multiple, extrahepatic, or vascular invasion-associated recurrence.
†Solitary and intrahepatic recurrence without vascular invasion.

**Table 3. Postoperative Liver Function**

| Variables | UFT (n = 79) | Control (n = 80) | P |
|---|---|---|---|
| Serum albumin after surgery (g/dL) | 3.8 (2.5-4.6) | 3.8 (3.1-4.6) | .06 |
| Serum ALT after surgery (IU/L) | 40 (14-144) | 49 (11-298) | .45 |
| Serum total bilirubin after surgery (mg/dL) | 0.8 (0.4-2.3) | 0.7 (0.3-2.1) | .05 |

NOTE. Data are shown as median with range. Data were obtained 1 year after surgery or before treatment for recurrence.

Contrary to expectations, overall survival appeared to be worse in the UFT group than in the control group, despite identical recurrence-free survival curves. These seemingly paradoxical results might be attributed to the difference between the groups in the pattern of recurrence, *i.e.*, advanced recurrence associated with vascular invasion, multiple tumors, and extrahepatic disease was more frequent in the UFT group. In fact, second resections, established as the most effective treatment for recurrent HCC,[14] were feasible in only 28% of the 58 patients with primary recurrence in the UFT group, as compared with 44% of the 57 patients with primary recurrence in the control group ($P = .08$, Table 2). These results suggest that UFT might have some potentially undesirable effects on HCC.

A previous study suggested that accelerated repopulation of surviving tumor cells can occur after sequential chemotherapy with 5-fluorouracil.[15] Although the causal relation between UFT and recurrence pattern is beyond the scope of our study, UFT may have promoted repopulation of HCC cells surviving in the microcirculation after surgery, thereby leading to the marginally higher incidence of advanced recurrence in the UFT group. Lai et al. reported that extrahepatic recurrence of HCC might be related to adjuvant chemotherapy with epirubicin.[16] However, further studies are needed to confirm these findings.

One reason for the poorer overall survival in the UFT group might be adverse effects of UFT on liver function. A previous study suggested that adjuvant chemotherapy (4′-epi-doxorubicin alone or in combination of UFT) after surgery for HCC might worsen overall survival in patients with cirrhosis by negatively affecting liver function.[17] In our study, however, the results of conventional liver function tests did not differ between the groups (Table 3), suggesting that adverse effects of UFT on liver function were negligible. To evaluate the clinical significance of UFT taking its possible effects on liver function into consideration, overall survival would be more suit-

able as the primary endpoint, because the patients have underlying liver disease and, unlike most cancers, a significant proportion of deaths in HCC patients are due to liver disease rather than to HCC.

Recently, UFT has received considerable attention as an effective anticancer drug.[8-11] The results of our clinical trial suggest that the effectiveness of UFT may have been overestimated in previous studies, perhaps because of publication bias. In patients undergoing surgery for HCC, however, our results offer no evidence to support potential benefits of adjuvant chemotherapy with UFT.

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ORIGINAL ARTICLE

# A phase II study of weekly irinotecan as first-line therapy for patients with metastatic pancreatic cancer

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**Abstract**
*Purpose* The aim of this study was to assess the efficacy and toxicity of weekly irinotecan in patients with metastatic pancreatic cancer.
*Patients and methods* Patients with histologically proven pancreatic adenocarcinoma, at least one bidimensionally measurable metastatic lesion, and no prior chemotherapy were selected. Irinotecan at a dose of 100 mg/m$^2$ was administered intravenously for 90 min on days 1, 8, and 15 every 4 weeks until disease progression or unacceptable toxicity. Pharmacokinetics was examined on day 1 of the first cycle of treatment.
*Results* Thirty-seven of 40 enrolled patients were assessable for efficacy and toxicity. A partial response was obtained in 10 patients, giving an overall response rate of 27.0% (95% confidence interval 13.8–44.1%). The median overall survival was 7.3 months with a 1-year survival rate of 29.5%. Although toxicities were generally tolerated, one patient died of disseminated intravascular coagulation syndrome induced by neutropenia with watery diarrhea. Pharmacokinetic study showed that patients with biliary drainage seemed to have higher area under the concentration versus time curve for irinotecan and its metabolites compared with patients without biliary drainage.
*Conclusion* Single-agent irinotecan has significant efficacy for metastatic pancreatic cancer. The toxicity with this schedule appears manageable, though it must be monitored carefully.

**Keywords** Irinotecan · Phase II study · Pancreatic cancer · Chemotherapy · Pharmacokinetics

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## Introduction

Pancreatic cancer is a highly aggressive disease, with approximately 21,000 deaths annually in Japan [7]. While surgery remains the only potential curative option for this disease, the vast majority of patients unfortunately present with advanced, unresectable disease. Although it has been demonstrated that gemcitabine is

an effective tool for palliation of symptoms and prolonging survival in patients with advanced pancreatic cancer [2], single-agent gemcitabine has shown limited benefit, with objective response rates of less than 15% and a median overall survival of around 4–6 months [2, 4, 5]. Therefore, there is a clear need to identify a new effective chemotherapeutic regimen for pancreatic cancer.

Irinotecan is a water-soluble semisynthetic derivative of camptothecin, a plant alkaloid obtained from the *Camptotheca acuminata* tree. Irinotecan and its active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), bind to topoisomerase I (an enzyme required for unwinding of DNA during replication), inducing double-stranded DNA breaks and consequent tumor cell death. Irinotecan is internationally approved for use in metastatic colorectal cancer, and has broad activity against other malignancies including lung cancer [6, 9, 15, 16]. Although several studies of single-agent irinotecan or irinotecan-based chemotherapy against pancreatic cancer have been reported [11, 12, 14, 18, 22], the role of irinotecan in the treatment of patients with pancreatic cancer remains unclear yet. Because there are few effective agents for pancreatic cancer to date, it is important to determine the clinical efficacy of irinotecan for this disease. We, therefore, conducted an open-label, multicenter, single-arm phase II study to evaluate the efficacy and toxicity of single-agent irinotecan in patients with pancreatic cancer. In the current study, we adopted weekly administration of irinotecan because safety of this schedule has been confirmed in other cancers in Japan [6, 9, 16]. Since patients with pancreatic cancer tend to suffer various tumor-related complications such as obstructive jaundice and impaired liver function, pharmacokinetic study was also performed.

## Patients and methods

### Patient selection

Patients were entered into the study if they fulfilled the following eligibility criteria: histologically or cytologically confirmed adenocarcinoma of the pancreas; at least one bidimensionally measurable metastatic lesion; no history of prior chemotherapy or radiotherapy; age 20–74 years; Karnofsky performance status (KPS) $\geq 50$ points; estimated life expectancy $\geq 2$ months; adequate bone marrow function (WBC count $< 12{,}000$ per $mm^3$, neutrophil count $\geq 2{,}000$ per $mm^3$, platelet count $\geq 100{,}000$ per $mm^3$, and hemoglobin level $\geq 10.0$ g/dl), adequate renal function (serum creatinine and blood urea nitrogen level $\leq$ the institutional upper limit of normal), and adequate liver function (serum total bilirubin level $\leq 2.0$ mg/dl, serum transaminases levels $\leq 2.5$ times the institutional upper limit of normal); and written informed consent. Patients were excluded if there was a history of severe drug hypersensitivity; serious complications; central nervous system metastases; other concomitant malignant disease; marked pleural or peritoneal effusion; and watery diarrhea. Pregnant or lactating women were also excluded. The study was performed in accordance with the Declaration of Helsinki, approved by the institutional review board of each participating center, and conducted in accordance with Good clinical practice guideline in Japan.

### Treatment plan

This study was an open-label, multicenter, single-arm phase II study. Irinotecan was supplied by Daiichi Pharmaceutical Co., Ltd. (Tokyo, Japan) and Yakult Honsha Co., Ltd. (Tokyo, Japan). Irinotecan at a dose of 100 mg/$m^2$ was administered intravenously for 90 min on days 1, 8, and 15 every 4 weeks until the occurrence of disease progression, unacceptable toxicity, or the patient's refusal to continue. Prophylactic administration of antiemetic agents was allowed at the investigator's discretion. Physical examination, complete blood cell counts, biochemistry tests, and urinalysis were assessed weekly during treatments. If patients experienced neutropenia of $< 1{,}500$ per $mm^3$, thrombocytopenia of $< 100{,}000$ per $mm^3$, fever ($\geq 38$°C) with suspected infection, grade $\geq 1$ or watery diarrhea, or $\geq$ grade 3 non-hematological toxicities other than nausea, vomiting and anorexia, irinotecan administration was omitted on that day and postponed to the next scheduled treatment day. If patients experienced neutropenia of $< 500$ per $mm^3$, thrombocytopenia of $< 50{,}000$ per $mm^3$, fever ($\geq 38$°C) with suspected infection, or grade $\geq 2$ or watery diarrhea at any time, the irinotecan dose of the subsequent cycle was reduced by 20 mg/$m^2$. Patients went off study if they required more than two dose reductions. If the next cycle could not start within 4 weeks from the scheduled day, the patient was withdrawn from the study. The toxicity of irinotecan therapy was evaluated according to the National Cancer Institute Common Toxicity criteria version 2.0.

### Evaluation

Objective tumor response was evaluated every 4 weeks according to the Japan Society for Cancer Therapy (JSCT) criteria [8], which is similar to the WHO crite-

ria. A complete response (CR) was defined as the disappearance of all evidence of cancer for at least 4 weeks. A partial response (PR) was defined as a $\geq 50\%$ reduction in the sum of the products of the two longest perpendicular diameters of all measurable lesions for at least 4 weeks without any evidence of new lesions. No change (NC) was defined as a $< 50\%$ reduction or a $< 25\%$ increase in the sum of the products of the two longest perpendicular diameters of all measurable lesions for at least 4 weeks without any evidence of new lesions. Progressive disease (PD) was defined as a $\geq 25\%$ increase or the appearance of new lesions. Primary pancreatic lesions were considered to be assessable but not measurable lesions, because it is difficult to measure the size of primary pancreatic lesions accurately [1]. Objective tumor response was secondarily assessed according to the response evaluation criteria in solid tumors (RECIST criteria) [20] among patients with at least one measurable metastatic lesion whose longest diameter measured by CT is no less than double the slice thickness. An external review committee confirmed objective responses and toxicities.

Clinical benefit was evaluated on the basis of established criteria [13]. Each patient was classified as a clinical benefit responder or non-responder on the basis of the change in two parameters of clinical benefit (pain and KPS). In the current study, the body weight was not used to evaluate clinical benefit response because the body weight of patients with pancreatic cancer sometimes increases due to not only improvement of their condition but also retention of malignant ascites. A positive response for pain was defined as an improved pain intensity of $\geq 50\%$ from baseline for $\geq 4$ weeks, or a decreased morphine consumption of $\geq 50\%$ from baseline for $\geq 4$ weeks. A positive response for KPS was defined as an improved KPS of $\geq 20$ points from baseline for $\geq 4$ weeks. To be classified as a clinical benefit responder, a patient had to achieve a positive response in at least one parameter (pain or KPS) without being negative for the other, sustained for $\geq 4$ weeks.

### Pharmacokinetics

To investigate the impact of biliary drainage on pharmacokinetics of irinotecan, we planned to recruit five patients each with and without biliary drainage. Heparinized blood samples (5 ml) for the pharmacokinetic study were obtained before infusion of irinotecan, at the end of the 90 min infusion, and 0.5, 1, 2, 4, 6, 8, 24 h after the completion of infusion on day 1 of the first cycle. Blood samples were immediately centrifuged at 3,000 rpm for 10 min to remove plasma and stored in polyethylene tubes at −20°C until analysis. Quantitative analysis of total irinotecan and its metabolites, SN-38, SN-38 glucuronide, and 7-ethyl-10-[4-*N*-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin (APC) was performed by methods previously described [17, 19].

### Statistical analysis

The primary goal was to evaluate the response rate (CR and PR) of irinotecan. The 95% confidence interval for response rate was calculated based on the binomial distribution. The response duration was defined as the interval from the first documentation of response to the first documentation of tumor progression. The time to progression (TTP) was calculated from the date of study enrollment to the first documentation of tumor progression; and overall survival was calculated from the date of study enrollment to the date of death or the last follow-up with censored value. Median overall survival and the median TTP were estimated by the Kaplan–Meier method and 95% confidence interval were estimated based on the Greenwood's formula. A total of 35 patients were planned to be enrolled based on the assumptions that the expected response rate of irinotecan was 15% and the threshold rate was 5%. A two-stage design was used in this study. The interim analysis was planned when 15 patients were enrolled in the first stage of the study. If the upper limit of the 90% confidence interval (one-sided) did not exceed the expected rate of 15% (no objective response in the 15 patients), irinotecan was judged to be ineffective and the study was ended. If an objective response was observed in any of the first 15 patients, additional 20 patients were enrolled in the second stage of accrual to estimate the response rate. If 6 or more out of 35 patients achieved objective response, the lower limit of the 95% confidence interval (two-sided) exceeds the threshold rate of 5%, and then the agent would be considered to be active for metastatic pancreatic cancer.

## Results

### Patients

Forty patients were enrolled in the study by 7 institutions between August 2001 and November 2002. Of the 40 patients, 3 patients who did not receive irinotecan because of rapid tumor progression or protocol violation were excluded from analysis. Patient characteristics of the remaining 37 patients are listed in Table 1.

All 37 patients had metastatic disease and had a good KPS of ≥ 80. Morphine was prescribed for 10 patients due to abdominal or back pain and 14 patients were assessable for clinical benefit response. Seven patients had recurrent disease after pancreatic resection. Two patients underwent percutaneous transhepatic biliary drainage for obstructive jaundice prior to study enrollment.

## Treatments

Data were collected through May 4, 2004, providing 18 months of survival follow-up from the time accrual ended. Thirty-seven patients were given a total of 108 cycles of therapy, with a median of 2 cycles each (range 1–10). The administration of irinotecan on day 8 and day 15 was performed in 87 (80.6%) and 76 (70.4%) of 108 cycles, respectively. Dose reduction was required in 13 patients (35.1%), mainly due to diarrhea and fever with suspected infection. At the time of analysis, all patients had discontinued the study because of disease progression ($n = 28$), toxicity ($n = 5$), treatment-related death ($n = 1$), and withdrawal of consent due to other reasons ($n = 3$). After discontinuation of irinotecan, 26 patients received gemcitabine monotherapy or gemcitabine-based combination therapy; one patient was treated with S-1, and remaining 10 patients underwent only supportive care. Among 27 patients treated with second-line chemotherapy, 2 patients who received gemcitabine monotherapy achieved a PR.

**Table 1** Patient characteristics ($n = 37$)

| Characteristics | | No. of patients (%) |
|---|---|---|
| Gender | | |
| Male | | 25 (67.6) |
| Female | | 12 (32.4) |
| Median age, years (range) | 59 (41–74) | |
| Karnofsky performance status, point | | |
| 100 | | 8 (21.6) |
| 90 | | 25 (67.6) |
| 80 | | 4 (10.8) |
| Median body surface area ($m^2$) (range) | 1.55 (1.31–1.85) | |
| History of surgical resection | | 7 (18.9) |
| PTBD | | 2 (5.4) |
| Sites of metastasis | | |
| Liver | | 33 (89.2) |
| Lymph nodes | | 17 (45.9) |
| Lung | | 8 (21.6) |
| Others | | 3 (8.1) |

*PTBD* percutaneous transhepatic biliary drainage

## Efficacy

Of 37 patients, 10 patients achieved a PR according to the JSCT criteria (Table 2). The overall response rate was therefore 27.0% (95% confidence interval 13.8–44.1%) with median response duration of 4.1 months (range 0.9–7.1 months). The median TTP was 2.1 months (range 0.7–9.5 months), and the median overall survival of 7.3 months (range 0.7–25.9 months) with a 1-year survival rate of 29.5% (Fig. 1). Of 29 patients assessable for RECIST criteria, a PR was seen in 8 patients (27.6%), stable disease in 6 patients (20.7%), and PD in 12 patients (41.4%). With regard to clinical benefit, 2 of 14 evaluable patients had pain relief and were classified as a responder (Table 3).

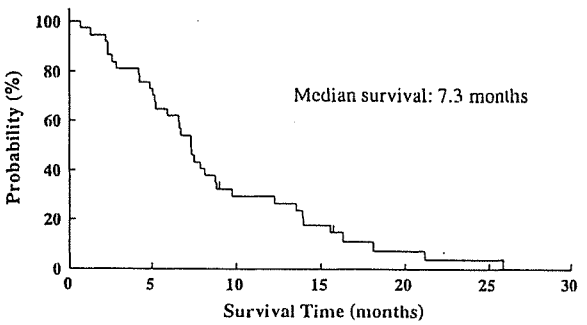


**Fig. 1** Overall survival curve of all 37 patients

**Table 2** Efficacy results

| | No. ($N = 37$) | % |
|---|---|---|
| Tumor response | | |
| Partial response | 10 | 27.0 |
| No change | 7 | 18.9 |
| Progressive disease | 17 | 45.9 |
| Not evaluable | 3 | 8.1 |
| Time to progression (months) | | |
| Median | 2.1 | |
| Range | 0.7–9.5 | |
| Overall survival (months) | | |
| Median | 7.3 | |
| Range | 0.7–25.9 | |
| 1-year survival rate | | 29.5 |

**Table 3** Clinical benefit response ($n = 14$)

| | | Karnofsky performance status | | |
|---|---|---|---|---|
| | | Improved | Stable | Worse |
| Pain | Improved | 0 | 2 | 0 |
| | Stable | 0 | 6 | 1 |
| | Worse | 0 | 5 | 0 |

### Toxicity

All 37 patients were assessable for toxicity. The major toxicities observed during the study are summarized in Table 4. The most common toxicities were hematological toxicity and gastrointestinal toxicity. Grade 3 or 4 neutropenia occurred in 10 patients (27.0%) and 5 patients received granulocyte-colony stimulating factors. The neutrophil count nadir typically occurred on day 21, and recovered to baseline values by day 28. Although nausea, vomiting, and anorexia were observed frequently, most of these toxicities recovered spontaneously or with adequate supportive treatment. Grade 3 diarrhea occurred in four patients and they were treated with loperamide. Most diarrheas appeared during the first cycle of treatment: the median time to the worst day of diarrhea was 13 days from the initiation of a cycle of therapy. Though the toxicities were mild to moderate in severity and short in duration, one patient died at day 21 of the first cycle of treatment because of disseminated intravascular coagulation syndrome and multiple organ failure induced by neutropenia and watery diarrhea due to irinotecan. The patient, a 58-year old woman with pretreatment KPS of 100, developed grade 4 neutropenia on day 12 complicated by fever (38.8°C) and grade 3 diarrhea that evolved to fatal shock despite aggressive medical management.

**Table 4** Treatment-related adverse events ($n = 37$): worst grade reported during treatment period

| Toxicity | Grade | | | | Grade 1–4 (%) | Grade 3–4 (%) |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | | |
| Hematologic | | | | | | |
| Leukopenia | 15 | 6 | 8 | 1 | 81.1 | 24.3 |
| Neutropenia | 5 | 11 | 8 | 2 | 70.3 | 27.0 |
| Anemia | 0 | 14 | 3 | 0 | 45.9 | 8.1 |
| Thrombocytopenia | 1 | 1 | 1 | 1 | 10.8 | 5.4 |
| Non-hematologic | | | | | | |
| Nausea | 7 | 12 | 15 | – | 91.9 | 40.5 |
| Vomiting | 7 | 14 | 5 | 0 | 70.3 | 13.5 |
| Diarrhea | 15 | 8 | 4 | 0 | 73.0 | 10.8 |
| Constipation | 1 | 8 | 2 | 0 | 29.7 | 5.4 |
| Anorexia | 4 | 7 | 14 | 1 | 70.3 | 40.5 |
| Stomatitis | 2 | 0 | 0 | 0 | 5.4 | 0 |
| Rash | 1 | 0 | 0 | 0 | 2.7 | 0 |
| Alopecia | 24 | 1 | – | – | 67.6 | – |
| Fatigue | 3 | 8 | 1 | 1 | 35.1 | 5.4 |
| Fever | 3 | 1 | 0 | 0 | 10.8 | 0 |
| Infection | 2 | 1 | 4 | 1 | 21.6 | 13.5 |
| Total bilirubin | 4 | 1 | 1 | 0 | 16.2 | 2.7 |
| AST | 5 | 5 | 2 | 0 | 32.4 | 5.4 |
| ALT | 4 | 4 | 3 | 0 | 29.7 | 8.1 |
| Hyponatremia | 6 | 0 | 3 | 0 | 24.3 | 8.1 |
| Creatinine | 0 | 0 | 2 | 0 | 5.4 | 5.4 |

*AST* aspartate aminotransferase, *ALT* alanine aminotransferase

### Pharmacokinetics

A pharmacokinetic analysis was performed in five patients without biliary drainage and in two patients who underwent percutaneous transhepatic biliary drainage (Planned five patients could not be enrolled in drainage group because only two patients had biliary drainage in the current study). Table 5 and Fig. 2 show the pharmacokinetic parameters for irinotecan and its three major metabolites in patients with and without biliary drainage. Although it was difficult to assess the influence of biliary drainage in this study because of the small number of subjects analyzed, patients with biliary drainage seemed to have higher area under the concentration versus time curve for irinotecan and its metabolites compared with patients without biliary drainage.

## Discussion

The prognosis of the patients with pancreatic cancer remains poor even after a randomized study demonstrated survival advantage of gemcitabine against advanced pancreatic cancer, indicating necessity of new effective agents or combination regimens for this dismal disease. Irinotecan, which has a quite different mechanism from gemcitabine, has been considered one of the attractive agents for pancreatic cancer, since this agent has demonstrated substantial activity in various types of malignant tumor [6, 9, 15, 16]. The current multicenter phase II study was, therefore, conducted to evaluate the efficacy and toxicity of single-agent irinotecan in patients with metastatic pancreatic cancer.

In this study, we found that weekly irinotecan demonstrated a good overall response rate of 27.0% in 37 patients with metastatic pancreatic cancer. In addition, a relatively long median overall survival of 7.3 months was shown, though all patients in our study had metastatic disease. As to clinical benefit response, 2 of 14 patients achieved clinical benefit response. These results indicate that irinotecan has a substantial antitumor effect on pancreatic cancer.

The major toxicities of irinotecan that were seen in the study were myelosuppression and gastrointestinal toxicities, similar to the previous observation of irinotecan monotherapy in other cancers [6, 9, 16]. Most toxicity was mild to moderate, and manageable with conservative treatment. However, one patient died of disseminated intravascular coagulation syndrome and multiple organ failure induced by neutropenia and diarrhea. Pretreatment condition of this patient was good (KPS = 100), and it was difficult to predict these

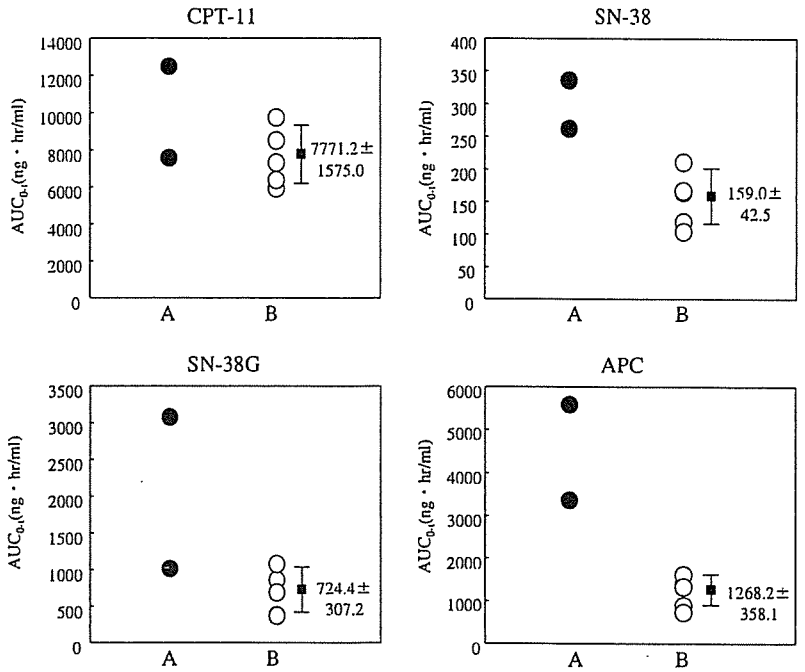


**Fig. 2** Area under the concentration versus time curve for irinotecan and metabolites in patients with biliary drainage ($A$, $n = 2$) and without drainage ($B$, $n = 5$). The values are expressed as the mean ± SD

**Table 5** Pharmacokinetic parameters after single administration of irinotecan at a dose of 100 mg/m$^2$ ($n = 7$)

| | | $C_{max}$ (ng/ml) | $T_{max}$ (h) | $T_{1/2}$ (h) | $AUC_{0-t}$ (ngh/ml) | CL (l/h m$^2$) |
|---|---|---|---|---|---|---|
| Irinotecan | A | 1,188.5, 1,997.6 | 1.6, 1.5 | 7.8, 8.2 | 7,762, 12,692 | 11.8, 7.1 |
| | B | 1,701.0 ± 348.3 | 1.5 ± 0.1 | 7.7 ± 0.9 | 7,771.2 ± 1,575.0 | 12.4 ± 2.5 |
| SN-38 | A | 25.5, 26.2 | 2.1, 1.5 | 14.7, 9.9 | 268, 342 | – |
| | B | 17.5 ± 3.8 | 2.3 ± 0.8 | 30.2 ± 27.6 | 159.0 ± 42.5 | |
| SN-38G | A | 81.3, 207.2 | 3.6, 2.0 | 10.8, 12.5 | 1,063, 3,130 | – |
| | B | 78.8 ± 34.1 | 2.2 ± 0.2 | 21.6 ± 13.2 | 724.4 ± 307.2 | |
| APC | A | 309.2, 359.3 | 2.6, 5.5 | 7.0, 9.5 | 3,441, 5,673 | – |
| | B | 116.6 ± 39.7 | 3.0 ± 0.6 | 8.8 ± 0.7 | 1,268.2 ± 358.1 | |

*A* Patients with biliary drainage $n = 2$

*B* Patients without biliary drainage (parameters are represented as the mean ± SD) $n = 5$

episodes before onset. Although our study indicated that weekly irinotecan administration would be tolerable in patients with metastatic pancreatic cancer, careful observation is required during the treatment period, since pancreatic cancer patients tend to suffer various tumor-related complications and easily take a turn to the worse because of tumor progression.

There are two studies of single-agent irinotecan that assessed efficacy and toxicity against pancreatic cancer [14, 22]. Sakata et al. [14] studied irinotecan at a dose of 100 or 150 mg/m$^2$ administered weekly or bi-weekly to previously treated or untreated patients with pancreatic cancer in Japan. Although 57 of 61 enrolled patients were assessable, only 4 patients (7.0%) showed a PR. This study included 28 patients (49.1%) with poor performance status of 2–3 and 22 patients (38.6%) with prior chemotherapy, and no patient showed a PR in these patients with poor performance status or prior chemotherapy. Wagener et al. [22] demonstrated that irinotecan at a dose of 350 mg/m$^2$ administered every 3 weeks to chemo-naïve pancreatic cancer patients with performance status of $\leq 2$, achieved a PR in 3 of 32 assessable patients (9.4%) with an median overall survival of 5.2 months. Although precise reason for the discrepant response rates between our study and the other two studies is unclear, patient background may be one possible explanation because only chemo-naïve patients with good performance status were entered into our study (89.2% of our patients had good KPS of $\geq 90$).

For the purpose of the improvement on response rate and prognosis, several studies of combination therapy have been conducted in patients with pancreatic cancer. With regard to irinotecan with gemcitabine, an