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Combination of Pre-Treatment DWI-Signal Intensity and S-1 Treatment: A Predictor of Survival in Patients with Locally Advanced Pancreatic Cancer Receiving Stereotactic Body Radiation Therapy and Sequential S-1

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Abstract

OBJECTIVE: To identify whether the combination of pre-treatment radiological and clinical factors can predict the overall survival (OS) in patients with locally advanced pancreatic cancer (LAPC) treated with stereotactic body radiation and sequential S-1 (a prodrug of 5-FU combined with two modulators) therapy with improved accuracy compared with that of established clinical and radiologic risk models. *METHODS:* Patients admitted with LAPC underwent diffusion weighted imaging (DWI) scan at 3.0-T ($b = 600$ s/mm^2). The mean signal intensity ($SI_b = 600$) of region-of-interest (ROI) was measured. The Log-rank test was done for tumor location, biliary stent, S-1, and other treatments and the Cox regression analysis was done to identify independent prognostic factors for OS. Prediction error curves (PEC) were used to assess potential errors in prediction of survival. The accuracy of prediction was evaluated by Integrated Brier Score (IBS) and C index. *RESULTS:* 41 patients were included in this study. The median OS was 11.7 months (2.8-23.23 months). The 1-year OS was 46%. Multivariate analysis showed that pre-treatment $SI_b = 600$ value and administration of S-1 were independent predictors for OS. The performance of pre-treatment $SI_b = 600$ and S-1 treatment in combination was better than that of $SI_b = 600$ or S-1 treatment alone. *CONCLUSION:* The combination of pre-treatment $SI_b = 600$ and S-1 treatment could predict the OS in patients with LAPC undergoing SBRT and sequential S-1 therapy with improved accuracy compared with that of established clinical and radiologic risk models.

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Introduction

As a more aggressive treatment modality, stereotactic body radiation therapy (SBRT) has emerged to be a preferred choice in the management of patients with LAPC who are not suitable for surgical resection. Compared to conventional radiotherapy, the radiation dose of SBRT can be delivered to the tumor with more precision and limited fractions, while the adjacent normal tissues can be protected to the largest extent. Moreover, as an important technique of SBRT, CyberKnife (Accuracy, Sunnyvale, CA, USA) is able to track the

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Table 1. Main Scanning parameters for All MR Sequences

Sequences	TR/TE (msec)	FOV (cm×cm)	Matrix	Thickness/Gap (mm)	Flip Angle (^{0})	Slices	NEX*	Bandwidth (KHz)	Speed Factor
2D Single-Shot Fast Spin Echo, SSFSE (MRCP)	7000/1200	30×30	288×288	50	-	6	0.92	31.25	-
LAVA	4.3/1.3	44×40	320×224	5	12	-	1	166.67	1.79
T2WI	6316/72	38×38	330×192	5	90	22	2	83.33	1.25
SS-EPI DWI	6000/56.5	38×30	96×128	5	90	25	b_0, 1; b_{600}, 4	250	2

motion of lesions and make real-time location adjustments accordingly, thus avoiding the inaccurate delivery due to motion of the abdominal organs during the respiratory cycle. In pancreatic cancer, CyberKnife has been reported to have excellent safety and efficacy profiles [1–3]. S-1, a prodrug of 5-FU, was an alternative to gemcitabine therapy for locally advanced or metastatic pancreatic cancer [4,5]. Compared to gemcitabine alone, it was demonstrated to have better objective response rates, similar OS and progression-free survival (PFS) rates, and comparable adverse effects [6]. Recently, the combination of S-1 and radiotherapy has been more and more widely applied for the treatment of pancreatic cancer. However, few studies have investigated the effect of SBRT combined with S-1 regimens [7–12] on patients with LAPC who are not indicated for surgery.

Morphological imaging techniques of MRI are hampered by the delay of assessment timing when the poor performance status appears and the judgment of disease progression is delivered. Diffusion-weighed imaging (DWI) is a noninvasive functional magnetic resonance imaging technique. Apparent diffusion coefficient (ADC), the quantitative parameter of DWI, has been widely used in the diagnosis and assessment of pancreatic cancer [13–16], but its effect remains controversial due to the subtle variations in the size and position of the region of interest (ROI) and imaging acquisition parameters [17–20]. Pancreatic cancer areas generally have a relatively high cellular component with abundant fibrosis, representing a higher SI compared with the surrounding non-neoplastic tissues on functional DWI. Thus, it is reasonable to assume that tumor measurements based on the parameter DWI-SI may be more accurate than morphological MRI and DWI-SI has been proved an useful biomaker in predicting clinical outcomes in locally advanced rectal cancer [21]. Hence, this study aims to identify whether the combination of pre-treatment DWI-SI and clinical risk factors can predict the OS for locally advanced pancreatic cancer (LAPC) with improved accuracy compared with other established clinical and radiologic risk models.

Methods and Materials

Patients

All volunteer patients provided written informed consent, and the study was approved by the clinical research ethics committee of Changhai hospital (No.CHEC-2016-032-01). From 2015 to 2017, 41 consecutive patients were enrolled into the study and their written informed consent to participate in the study was obtained prior to MRI acquisition. All included patients should meet the following criteria: 1) had pancreatic cancer without distant metastasis proved by positron emission tomography-computed tomography (PET-CT) prior to MRI scan; 2) had no contraindications to MRI scan, including implanted metal foreign bodies, claustrophobia, and certain types of cardiac pacemaker; 3) had no allergy to gadolinium-based contrast agent; 4) had not received any other anticancer treatment prior to CyberKnife therapy.

MRI

All examinations were performed on a 3.0-Tesla MR (Signa HDxt V16.0, GE Healthcare, Milwaukee, WI, USA) with an eight-element phased array coil. All participants received MRI scans with standard protocols including transverse respiratory triggered single-shot echo-planar DWI with a b value of 600s/mm2. Selective presaturation with inversion recovery (SPIR) was used for fat saturation, and two saturation slabs were fixed on the anterior/posterior direction to reduce potential motion artifacts. Main scan parameters of MRI sequences were listed in Table 1. All patients underwent contrast-enhanced liver acceleration volume acquisition (LAVA) after gadopentetate dimeglumine injection (physiological saline, 10-15 ml; media, 0.1-0.15 mmol/kg; injection rate, 2-3 ml/s) at the end of the study.

Treatment Regimens

Patients were immobilized at the supine position with a vacuum bag. Spiral computed tomography (CT) was performed with slice thickness of 1.5 mm. Gross tumor volume (GTV) was depicted as a radiographically evident gross disease by contrast CT. The clinical target volume (CTV) including areas of the potential subclinical disease spread was also designated at the discretion of the physicians. In the majority of patients, the CTV was equaled to GTV. A 2- to 5-mm expansion margin was encompassed to determine the planning target volume (PTV). The total dose varied from 30 to 36 Gy in five to six fractions. Normal tissue constraints were referred to the American Association of Physicists in Medicine guidelines in TG-101 [22], as presented in Tables 2 and 3. More than 90% of PTV should be encompassed by the prescription of isodose line. The X sight Spine Tracking System and fiducials were used for motion tracking. After radiotherapy, 2 or 3 cycles of S-1 were sequentially given with an

Table 2. Serial Organs and Threshold Doses

Serial Organs	Threshold doses (Five Fractions)	Max Point Dose	Max Critical Volume Above Threshold
Spinal cord	23 Gy	30 Gy	0.35 cc
Duodenum	18 Gy	32 Gy	5 cc
Bowel	19.5 Gy	35 Gy	5 cc
Stomach	18 Gy	32 Gy	10 cc
Esophagus	19.5 Gy	35 Gy	5 cc
Colon	25 Gy	38 Gy	20 cc

Table 3. Parallel Organs and Threshold Doses

Parallel Organs	Threshold Doses (Five Fractions)	Minimum Critical Volume Below Threshold
Liver	21 Gy	700 cc
Kidney	17.5 Gy	200 cc

Table 4. The Characteristics of Patients

Items	N(Missing)	Mean(SD)	Median	Q1*,Q3*	Min, Max
Age(year)	41(0)	61.98±11.62	64.00	51.00,70.00	44.00,80.00
Size(cm)	41(0)	3.92±1.42	3.70	3.20,4.20	1.60,8.20
DWI-SI	41(0)	519.94 ±168.18	1.49	411.55,564.40	313.27,1243
CA19-9(IU/ml)	41(0)	616.17±505.77	500.00	100.00,1200.00	2.00,1600.00
Time(days)	41(0)	349.90±163.85	352.00	206.00,479.00	84.00,697.00
Gender (Male/Female)	28/13				
Location (Head/Body and tail)	34/7				
Biliary stent (Yes/No)	16/25				
S-1 (Yes/No)	32/9				
Other treatment (Yes/No)	11/30				
Status (Dead/Censor)	37/4				

Q1*: first quartile; Q3*: third quartile.

interval of 14 days. One cycle consisted of 28 days of oral S-1 at a dose of 80 mg/m2 for twice a day.

Data Collection

The region of interest (ROI) represents the largest single-slice area at the level of the maximum diameter of the tumor based on T2WI [23], excluding the pancreatic ducts, cystic lesions and necrosis. The areas of ROI in this study ranged from 101mm2 to 2970 mm2.

Statistical Analysis

Interclass correlation coefficient (ICC, value and strength of correlation are rated as follows: 0-0.20: poor correlation; 0.21-0.40: fair correlation; 0.41-0.60: moderate correlation; 0.61-0.80: good correlation; 0.81-1.00: excellent correlation) [24] was used to evaluate the agreement of SI_b = 600 measurement between two investigators. When the level of agreement was acceptable, the value rated by the first doctor was included for further analysis. Log-rank test was done

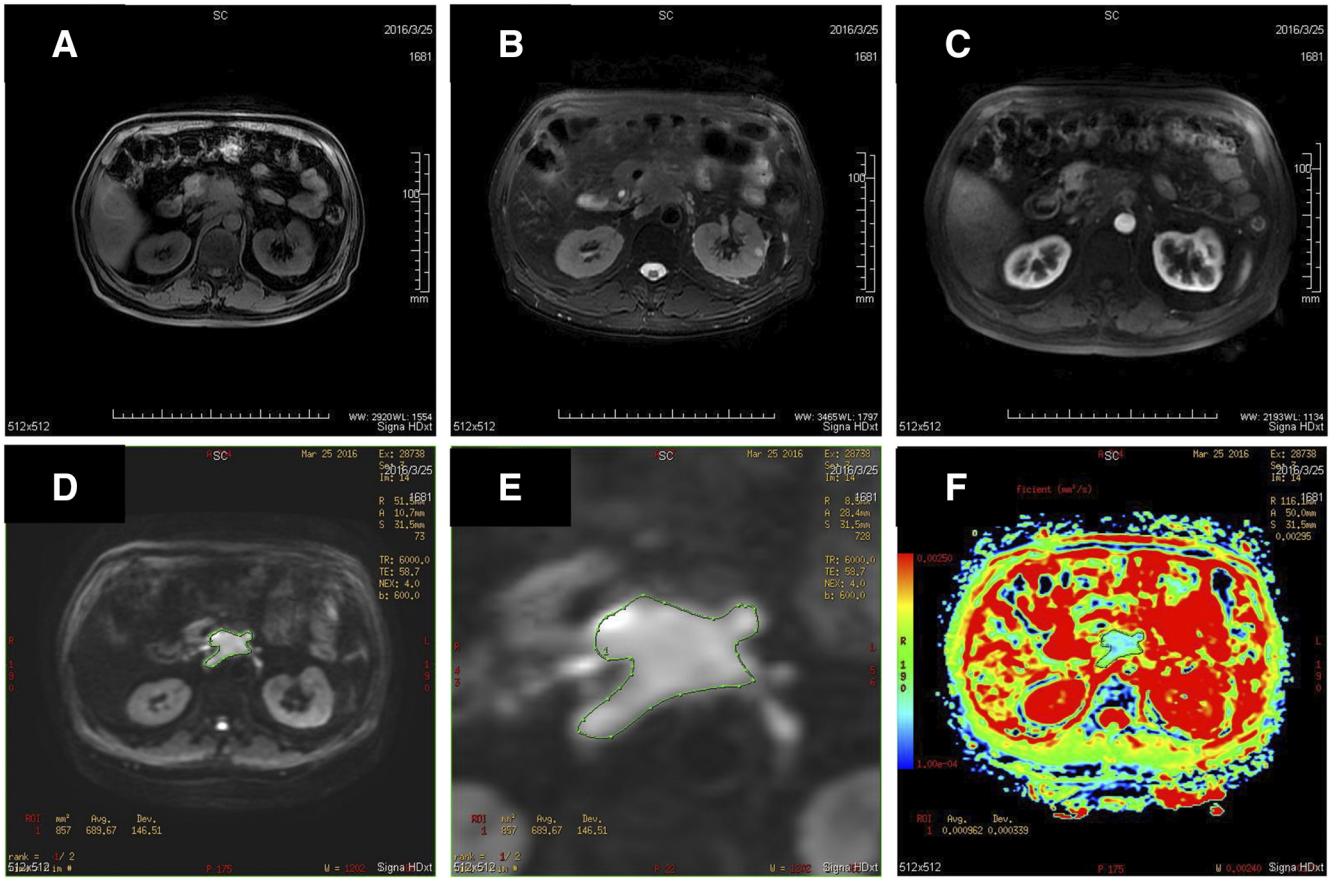

Figure 1. A 66-year-old male patient with adenocarcinoma in the head of the pancreas. The images showed the lesion with clearly demarcated area with hyperintensity compared to the surrounding normal tissues on DWI images. (A) Axial T1-weighted image. (B) Axial T2-weighted image. (C) Axial contrast-enhanced MRI image depicted a hypointense lesion at the head of the pancreas. (D) Freehand ROIs were drawn along the high signal intensity border of the tumor on obtained DWI images (b = 600s/mm^2). The slice was chosen to capture the largest cross-sectional tumor diameter on DWI maps (E: Magnification of lesion on DWI image; F: ADC map).

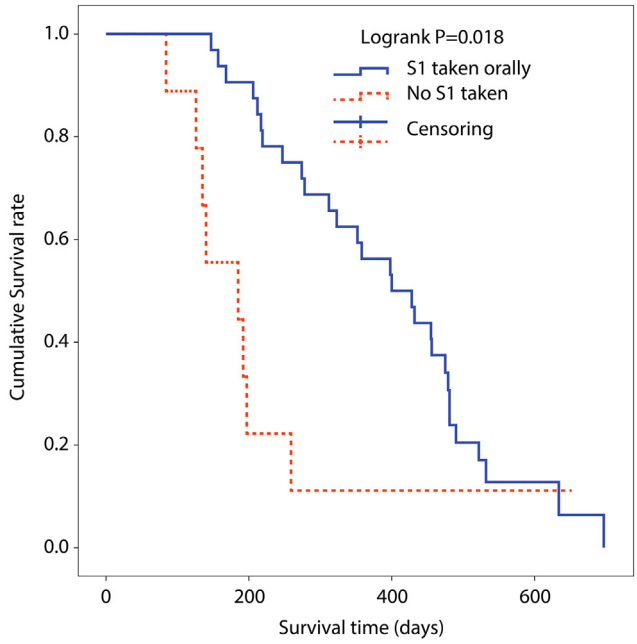

Figure 2. Patients with oral S-1 treatment had significantly longer OS compared with patients without S-1 (P = .018).

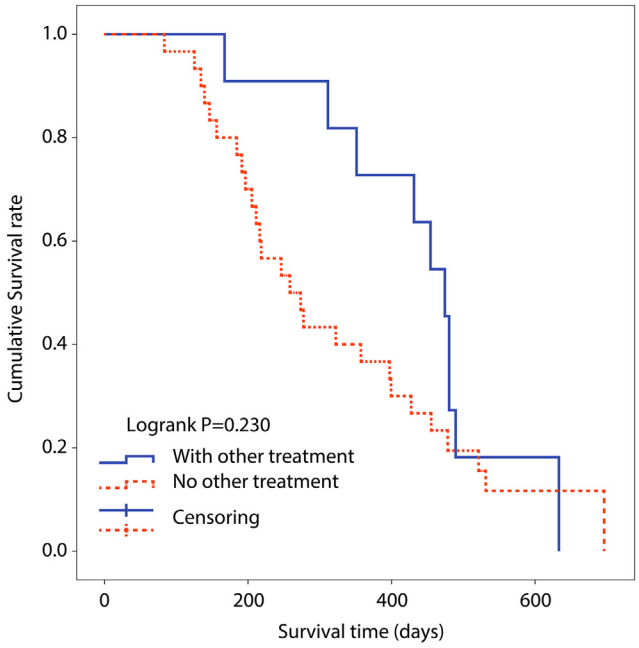

Figure 4. Patients who underwent other palliative treatments after metastasis tended to have a better OS (P = .23).

to compare the survivals between patients with different tumor location, and presence or absence of biliary stent, S-1, or other treatments. Prognostic factors of OS in patients with LAPC were identified by the Cox proportional hazard model. Prediction error curves (PEC) were used to assess the potential errors among OS predictors. $P < .05$ indicated a statistical significant level. The PEC curves were plotted by PEC package. All statistical analyses were performed with R software (www.r-project.org).

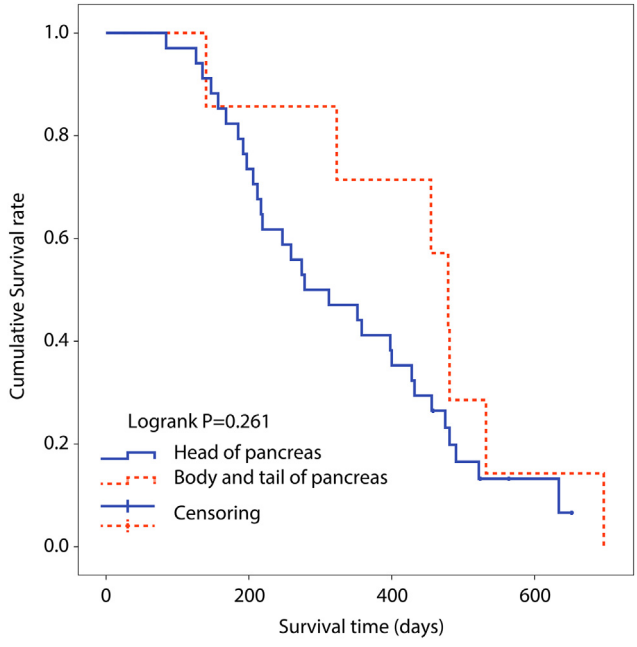

Figure 3. Patients with lesions located at the pancreatic body and tail trend to have longer OS than those at the pancreatic head (P = .261).

Results

Patient Characteristics

Demographic features and clinical characteristics of all the enrolled patients were listed in Table 4. Five patients were lost to follow-up during the period, and 41 patients (28 males and 13 females) with a median age of 64years (range, 44-80 years) were enrolled into this study. The median follow-up duration was 12.43 months (range, 2.8-24 months). The median tumor diameter was 3.7 cm (range, 1.6-8.2 cm). Sixteen patients had biliary stent implanted, 32 had oral S-1, 34 patients had lesions located at the pancreatic head and 11 had other treatments after tumor metastasis, including transcatheter arterial chemoembolization (TACE, n = 2), herbal antineoplastic agents (traditional Chinese medicine, n = 3), ablation therapy (n = 2), gemcitabine (n = 3), and I-125 seed implant (n = 1).These 11 patients were not further categorized according to the treatment they had due to the small sample in each modality. Up to August 31, 2017, 37 patients were dead and four patients were still alive.

Inter-Observer Variability of ADC Values

The typical axial DWI-MRI images and SI measurement were demonstrated in Figure 1. ICC showed good agreement between two investigators (ICC = 0.97). The mean ICC level was 4.21 (95% CI: −8.88 to 17.29).

OS and its Predicting Factors in Patients with LAPC

The 1-year OS rate among all enrolled patients was 46% (95% CI, 30%-62%). Patients with oral S-1 treatment had significantly longer OS compared with patients without S-1 (P = .018). Though there is no significant difference in OS between patients with lesions occurring in different parts of pancreas, patients with lesions located at the pancreatic body and tail trend to have longer OS than those at the pancreatic head (P = .261). In addition, patients who underwent other palliative treatments after metastasis tended to have a better OS (P = .23). There is

no significant difference in OS between patients with or without biliary sent (P = .799). (Figures 2-5). Multivariate analysis revealed that pre-treatment SI_b = 600 value (HR 0.995, 95% CI 0.992-0.998, P = .0002) and S-1 treatment (HR 0.09, 95% CI 0.032-0.254, P < .0001) were independent predicting factors for OS (Table 5). Additionally, in order to validate the accuracy of the prediction, the PEC model was assessed using both the integrated Brier score (IBS, lower values indicating better model performance) and C index (higher values indicating better discriminative ability). The performance of SI_b = 600 and S-1 in combination (IBS: 0.108, C index: 0.723) was better than that of SI_b = 600 or S-1 alone (IBS: 0.136, C index: 0.593; and IBS: 0.129, C index: 0.622, respectively, Figure 6).

Discussion

The main finding of this study is that the parameter pre-treatment DWI-SI and S-1 therapy are both independent prognostic factors for the OS of patients with LAPC, and the combination model of pre-treatment DWI-SI and S-1 as risk factor can predict the OS in LAPC patients treated with stereotactic body radiation and sequential S-1 therapy with better accuracy compared with pre-treatment DWI-SI or S-1 alone.

The two radiologists achieved a good agreement with an ICC of 0.97, suggesting good reliability and reproducibility of our data. In Cox regression analysis, pre-treatment SI_b = 600 was found to be significantly correlated with patient OS (HR 0.995, P = .0002, 95% CI 0.992-0.998), indicating that for each additional 1 of SI_b = 600, the risk of death is reduced by 0.005 times. Similarly, the mortality of patients who had S-1 was 0.09 times that of those who did not, which further confirmed the good clinical efficacy of S-1 reported previously [25,26]. Finally, prediction error curves generated by PEC model showed that the combination model of pre-treatment SI_b = 600 and S-1 performed better in predicting OS for LAPC, compared to SI_b = 600 or S-1 alone.

Table 5. Cox Regression Result for ADC (DWI)

Variables	β	χ^2	P	HR	%95 CI (Low, Up)
S-1	-2.40969	20.6132	<.0001	0.090	(0.032, 0.254)
SI(DWI)	-0.00506	13.5831	.0002	0.995	(0.992, 0.998)

Diffusion-weighted imaging (DWI) is a relatively new functional MRI technique used in many fields of tumors for its advantage in compensating the drawbacks of morphological MRI. ADC, as its quantitative parameter, has been widely used for the differential diagnosis of benign and malignant tumors and early detection of cancers, reflecting its importance in the diagnosis of tumors [13–16]. However, due to subtle variations in ROI size, ROI positioning, imaging acquisition parameters, ADC is not without its limitations and the results are often controversial and not satisfactory [17-20; 23]. Moreover, ADC measurement on DWI is relatively less practical for a routine clinical use because of the need for a specific workstation and a standard software package, as well as a time-consuming calculation process. Due to the higher cellular density and fibrotic component, pancreatic cancers usually present relatively higher SI compared with that of the surrounding non-neoplastic tissues on functional DWI images [20]. Thus, it can be assumed that the tumor measurements based on the DWI-SI series may be more accurate than that of morphological MRI [21]. Moreover, as a quantitative parameter, SI has its advantages in clinical practice: Firstly, the SI results the advantage of quantitative evaluation, which is considered to be objective; Secondly, its calculation are relatively more simple without the tedious measurement process as for ADC, thus avoiding error occurrence due to the mismatching of different b values between the same slice scanning. Thirdly, it is more cost-effective without the need for other sequences of pre-treatment MRIs, except for the T2-weighted images that are necessary for the identification primary tumor and the exclusion of pancreatic ducts, cystic lesions and

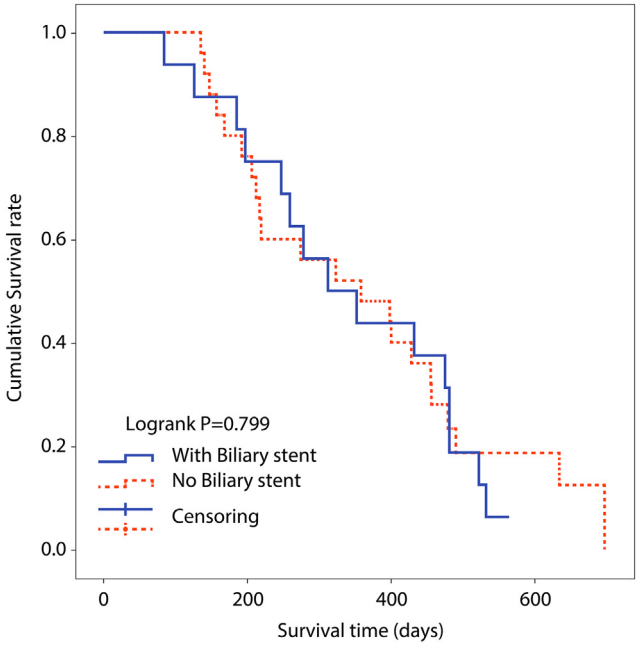

Figure 5. There is no significant difference in OS between patients with or without biliary sent (P = .799).

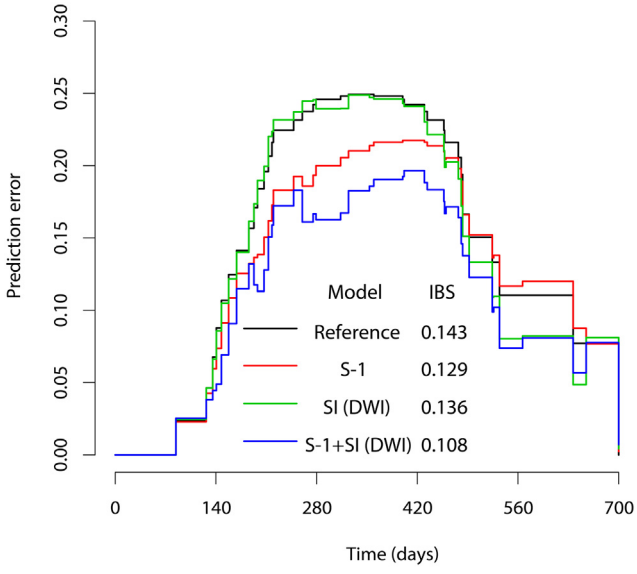

Figure 6. The performance of SI_b = 600 and S-1 in combination (IBS: 0.108, C index: 0.723) was better than that of SIb = 600 or S-1 alone (IBS: 0.136, C index: 0.593; and IBS: 0.129, C index: 0.622, respectively).

necrosis. In summary, the method of SI measurement on DWI we described is objective, feasible, and far less time consuming.

In addition to the characteristics of the tissue that would affect DWI-SI, DWI techniques can also have an influence on this quantitative parameter. The purpose of the respiratory triggering approach used in our abdominal MR imaging was to guarantee the quality of images and reliability of quantitative parameters [27]. Moreover, in order to reduce scan time, image distortion and artifact, the recommended *b* value was chosen as 600 s/mm^2 [28].

There are some limitations in the present study. The eligible patient number enrolled is relatively small regarding the statistical significance identified for patient OS and its predictors, such as tumor location and other treatments. Thus, future studies with larger sample size are warranted for the validation of our preliminary results.

In conclusion, the present study has demonstrated that the combination model of pre-treatment SI_b = 600 and S-1 could predict the OS of patients with LAPC undergoing SBRT followed by S-1 with improved accuracy compared with that of established clinical and radiologic risk models.

Conflict of Interest

All authors declare that they have no conflict of interest.

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Ethical Approval

The study was approved by the clinical research ethics committee of Changhai hospital (No.CHEC-2016-032-01). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Written informed consent was obtained from all patients before treatment. An additional individual consent for this analysis was not needed.

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