PUBLISHED VERSION

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Annals of Oncology, 2015; 26(7):1396-1401

Originally published at:
http://doi.org/10.1093/annonc/mdv180

Annals of Oncology

Annals of Oncology 26: 1396–1401, 2015
doi:10.1093/annonc/mdv180
Published online 17 April 2015

A refined risk stratification scheme for clinical stage 1 NSGCT based on evaluation of both embryonal predominance and lymphovascular invasion

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Received 31 July 2014; revised 2 September 2014 and 28 March 2015; accepted 7 April 2015

Background: Active surveillance is an increasingly accepted approach for managing patients with germ-cell tumors (GCTs) after an orchiectomy. Here we investigate a time-to-relapse stratification scheme for clinical stage 1 (CS1) nonseminoma GCT (NSGCT) patients according to factors associated with relapse and identify a group of patients with a lower frequency and longer time-to-relapse who may require an alternative surveillance strategy.

Patients and methods: We analyzed 266 CS1 GCT patients from the IRB-approved DFCI GCT database that exclusively underwent surveillance following orchiectomy from 1997 to 2013. We stratified NSGCT patients according to predominance of embryonal carcinoma (EmbP) and lymphovascular invasion (LVI), using a 0, 1, and 2 scoring system. Cox regression and conditional risk analysis were used to compare each NSGCT group to patients in the seminomatous germ-cell tumor (SGCT) category. Median time-to-relapse values were then calculated among those patients who underwent relapse. Relapse-free survival curves were generated using the Kaplan–Meier method.

Results: Fifty (37%) NSGCT and 20 (15%) SGCT patients relapsed. The median time-to-relapse was 11.5 versus 6.3 months for the SGCT and NSGCT groups, respectively. For NSGCT patients, relapse rates were higher and median time-to-relapse faster with increasing number of risk factors (RFs). Relapse rates (%) and median time-to-relapse (months) were 25%/8.5 months, 41%/6.8 months and 78%/3.8 months for RF_0, RF_1 and RF_2, respectively. We found a statistically significant difference between SGCT and patients with one or two RFs ($P < 0.001$) but not between SGCT and NSGCT RF_0 ($P = 0.108$).

Conclusion: NSGCT patients grouped by a risk score system based on EmbP and LVI yielded three groups with distinct relapse patterns -and patients with neither EmbP nor LVI appear to behave similar to SGCT.

Key words: nonseminoma germ-cell tumor, clinical stage 1, relapse, embryonal predominance, lymphovascular invasion, active surveillance

introduction

Germ-cell tumors (GCTs) account for 95% of malignant tumors of the testicle and are the most common solid tumor in men ages 15–34 years [1]. CS1 seminoma and nonseminomatous germ-cell tumor (NSGCT) have different propensities for relapse [2–4] and 54% of NSGCTs present with clinical stage 1 (CS1) disease defined as no tumor marker (TM) elevation or radiographic evidence of disease beyond the scrotum [5, 6]. Orchiectomy cures ~70% of NSGCT CS1 patients as 30% have occult metastasis and relapse [2]. The management options for CS1 NSGCT are nerve-sparing retroperitoneal lymph node dissection (RPLND), adjuvant chemotherapy and surveillance [6] with cure rates of 99% as salvage therapy cures nearly all patients who relapse on surveillance [1]. Seminomatous germ-cell tumors (SGCTs) present as CS1 in 75% of the cases and orchiectomy cures ~85% of these patients [3, 4]. The postorchiectomy management options for seminoma are adjuvant chemotherapy, adjuvant external beam radiation and surveillance with cure rates approximating 100% regardless of initial management [7].

Active surveillance entails the periodic assessment of TMs, CT of the abdomen and pelvis, and chest imaging in postorchiectomy

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patients, reserving additional treatment of those who relapse. Surveillance has been deemed an effective management strategy for CS1 GCTs even in patients with high-risk (~50%) chance of relapse, given the morbidity associated with primary RPLND or adjuvant chemotherapy given avoidance of overtreatment of those cured with orchiectomy alone and availability of successful salvaged therapy [5, 8]. Recent modeling research has shown that surveillance does not compromise life expectancy for patients with either SGCT or NSGCT [9].

Surveillance guidelines for diagnostic imaging are more intense for NSGCT than for seminoma patients given that the former has a higher risk of recurrence and a shorter time-to-relapse. Different pathological features identify NSGCT patients with higher risk of relapse with lymphovascular invasion (LVI) being regarded as the most consistent independent predictive factor of relapse [10, 11]. A high component of embryonal carcinoma is another factor reported to be associated with risk of relapse [11, 12].

Given the benefits of active surveillance, strategies that reduce ionizing radiation exposure while preserving the outcome benefits of surveillance could improve the care of these patients. One potential strategy is to stratify NSGCTs patients according to a risk factor (RF) scoring system that optimizes surveillance frequency for those with a low-risk and delayed time-to-relapse. In the present study, we carried out a retrospective survey to establish a time-to-relapse model in the first 2 years of surveillance for CS1 NSGCT patients according relapse-associated RFs, with particular emphasis on the first 6 months.

patients and methods

We identified 266 patients from the IRB-approved Dana-Farber Cancer Institute (DFCI) GCT database with CS1 disease who were managed with surveillance between 1997 and 2013. Clinical and pathological data collected included: age at orchiectomy, orchiectomy histology, level of preoperative TMs, presence/absence of LVI, embryonal predominance (EmbP), as well as postorchiectomy management information for the first 2 years and grouped by 3-month intervals. These included: number of AP-CTs (abdomino-pelvic computerized tomography excluding initial staging scan), TMs and follow-up visits. The Genitourinary Pathology Division of Brigham and Women's Hospital/DFCI carried out central pathology review before treatment recommendations, in accordance with institutional policy. A tumor was considered embryonal predominant if this component was present at a level larger than any other histologic type present on the sample. The frequency of surveillance with CT-AP, chest X-ray and TMs was decided by the treating physicians and in essence followed NCCN guidelines at relevant times [13].

The primary end point in this study was time-to-relapse from date of orchiectomy. To assess the relapse-predictive nature of our proposed model, we calculated hazard ratios (HRs) using the Cox regression proportional hazards model. A value of $P < 0.05$ was deemed statistically significant for multivariate modeling. Relapse-free survival (RFS) rates and incidence rates were calculated using the Kaplan–Meier method and conditional risk analysis was carried out using varying times of origin (t_0) at 0, 6, 12 and 18 months. Median time-to-relapse values were calculated after Cox regression among patients who relapsed. Finally, for model diagnostic purposes, the proportionality assumption was tested using Schoenfeld's scaled residuals and data goodness-of-fit was assessed using Cox-Snell residuals.

results

patient characteristics

The cohort consisted of 135 patients with NSGCT and 131 patients with seminoma ($n = 266$). Patient characteristics are described in Table 1. For NSGCT patients, there was no difference between LVI+ and LVI− in age, median follow-up time, median time-to-first surveillance scan, or surveillance metrics

Table 1. Patient characteristics and postorchiectomy surveillance

No. of patients	Full cohort	SGCT	NSGCT	NSGCT		P^a	NSGCT		P^a
				LVI+	LVI−		EmbP+	EmbP−	
	$N = 266$	$N = 131$	$N = 135$	$N = 22$	$N = 113$		$N = 55$	$N = 80$	
Median age at orchiectomy (range)	32 (17–66)	35 (17–66)	29 (17–64)	29 (18–60)	29 (17–64)	0.917	29 (18–55)	28 (17–64)	0.583
Median follow-up, months (range)	42 (1–264)	37 (1–264)	48 (2–222)	49 (9–163)	48 (2–222)	0.970	48 (3–174)	47 (2–222)	0.805
Surveillance metrics[b]	$n = 193$	$n = 103$	$n = 90$	$n = 15$	$n = 75$		$n = 37$	$n = 53$	
AP-CTs									
Median time to first surveillance scan (range)[c]	5 (1–20)	6 (2–20)	6 (1–11)	6 (2–11)	4 (1–9)	0.090	5 (1–11)	4 (1–9)	0.520
Median # AP-CTs by 6 months (range)	1 (0–4)	0 (0–2)	1 (0–4)	0 (0–4)	1 (0–3)	0.265	1 (0–4)	1 (0–3)	0.389
Median # AP-CTs by 12 months (range)	3 (0–7)	1 (0–4)	2 (1–7)	2 (1–7)	2 (1–5)	0.378	2 (1–7)	2 (1–5)	0.703
Tumor markers									
Median # TMs by 6 months (range)	1 (0–4)	1 (0–4)	3 (0–1)	2 (0–9)	4 (0–10)	0.450	3 (0–10)	3 (0–9)	0.967
Median # TMs by 12 months (range)	5 (0–16)	2 (0–8)	6 (1–16)	5 (1–13)	6 (2–16)	0.697	6 (1–12)	6 (2–16)	0.524
Surveillance visits									
Median # SVs by 6 months (range)	2 (0–7)	0 (0–4)	3 (0–7)	2 (0–5)	3 (0–7)	0.741	3 (0–6)	3 (0–7)	0.833
Median # SVs by 12 months (range)	5 (0–12)	2 (0–7)	5 (0–12)	5 (1–8)	5 (0–12)	0.145	5 (0–12)	5 (1–11)	0.703

[a]Nonparametric equality of medians test.
[b]The '*n*' value corresponds to the number of patients that had surveillance data available within each group.
[c]The first surveillance scan is actually the second scan after orchiectomy. The first AP-CT is considered a baseline staging scan and hence not included in surveillance regimen.
SGCT, seminoma; NSGCT, nonseminoma; LVI, lymphovascular invasion; EmbP, embryonal predominance; AP-CT, abdomino-pelvic computerized tomography scan; TMs, tumor markers; SV, surveillance visit.

Table 2. NSGCT risk factor score and risk of relapse

	No. of patients in group	No. of relapsed patients (relapse rate)	HR (95% CI)	P^a
SGCT	131	20/131 (15%)	1.0 (ref)	–
NSGCT RF_0	76	19/76 (25%)	1.67 (0.89–3.15)	0.108
NSGCT RF_1	41	17/41 (41%)	3.35 (1.75–6.40)	<**0.001**
NSGCT RF_2	18	14/18 (77%)	9.80 (4.91–19.56)	<**0.001**

[a]Cox regression analysis using SGCT as reference group.
SGCT, seminoma; NSGCT, nonseminoma; LVI, lymphovascular invasion; EmbP, embryonal predominance; RF_0, LVI− and EmbP−; RF_1, LVI or EmbP+; RF_2, LVI+ and EmbP+; HR, hazard ratio; CI, confidence interval.

Table 3. Conditional risk survival analysis by risk score category[a]

Time point (months)	Group	HR (95% CI)	P^a
0	RF_0	1.67 (0.89–3.15)	0.108
	RF_1	3.35 (1.75–6.40)	<**0.001**
	RF_2	9.80 (4.91–19.56)	<**0.001**
6	RF_0	1.33 (0.62–2.81)	0.463
	RF_1	2.35 (1.04–5.33)	**0.040**
	RF_2	5.76 (2.10–15.85)	**0.001**
12	RF_0	1.44 (0.56–3.69)	0.446
	RF_1	1.25 (0.34–4.55)	0.736
	RF_2	4.60 (0.99–21.3)	0.051
18	RF_0	1.57 (0.52–4.74)	0.426
	RF_1	1.78 (0.46–6.91)	0.404
	RF_2	3.67 (0.44–30.4)	0.228

[a]Cox regression with SGCT as reference group. The assessment was carried out at 0, 6, 12 and 18 months origin time points.
LVI, lymphovascular invasion; EmbP, embryonal predominance; RF_0, LVI− and EmbP−; RF_1, LVI or EmbP+; RF_2, LVI+ and EmbP+; HR, hazard ratio; CI, confidence interval.

(e.g. number of AP-CTs, TMs, visits). Similarly, no statistically significant difference was found between the EmbP+ and EmbP − groups in age median follow-up time median time-to-first surveillance scan or surveillance metrics.

NSGCT risk score stratification

Cox regression analysis was carried out to compare the RFS functions from each NSGCT RF score category against the SGCT group (Table 2) (RF_0 neither LVI nor EmbP, RF_1 one of either; RF_2 both present). We found a statistically significant difference for SGCT versus RF_1, SGCT versus RF_2 ($P < 0.001$, in both cases) but not for SGCT versus RF_0 ($P = 0.108$). Conditional risk survival analysis for each group using 0, 6, 12 and 18 months as origin time (t_0) found that RF_0 and SGCT were not significantly different in any of the recorded time points, while RF_1 and RF_2 ceased to be significantly different from SGCT at 12 and 18 months, respectively (Table 3) as most of the relapses happened by month 12.

relapse patterns and relapse-free survival

Relapse patterns for NSGCT and SGCT patients are described in Tables 4 and 5 and Figure 1. Fifty (37%) NSGCT and 20 (15%) SGCT patients relapsed. The median time-to-relapse was 11.5 versus 6.3 months for the SGCT and NSGCT groups, respectively. For NSGCT, relapse incidence was highest in the first 6-month interval (48% of all relapses) and the rate then progressively declined (26% more by year 1; 12% more by year 2). For SGCT, relapse incidence was highest in the second 6-month interval (30% versus 20% during the first 6 months), and then declined (15% more by year 2). Seven of 50 (14%) relapses took place after 2 years for NSGCT, compared with 7 of 20 (35%) relapses for seminomas. Of the 85 NSGCT patients who had not relapsed by year 5, 2.3% (2 of 85) subsequently relapsed. Of the 114 SGCT patients who had not relapsed by year 5, 2.6% (2 of 114) subsequently did.

For NSGCT patients, relapse rates were higher and median time-to-relapse faster with increasing number of RFs: relapse rates (%) and median time-to-relapse (months) were 25%/8.5 months, 41%/6.8 months and 78%/3.8months for RF_0, RF_1 and RF_2, respectively. Regarding disease-risk category at relapse, 94% of the 50 NSGCT relapses were classified as good-risk, while intermediate and poor-risk disease was found in two and one patients, respectively—13 of the 14 RF_2 patients who relapsed had good-risk metastatic disease and one had intermediate-risk disease. All RF_2 relapses occurred before 24 months. Of the 20 SGCT patients who relapsed, only one of 20 did not present with good-risk disease.

discussion

GCT worldwide incidence has more than doubled in the last 40 years, especially in industrialized countries [14]. The advent of successful salvage therapy, as well as the morbidity associated with other postoperative management options, has made active surveillance an acceptable management strategy [5]. In order to decrease the potential lifetime attributable risk of cancer incidence, modern surveillance regimens obtain fewer CTs, employ techniques aimed at limiting radiation to the minimum necessary for diagnostic purposes, or avoid altogether (i.e. MRI). The wide implementation MRI surveillance may be limited by the availability of appropriately experienced radiologists required to achieve the same sensitivity as CTs, and is the subject of an ongoing study [15].

Even with these modality improvements, active surveillance is associated with significant radiation exposure, which is particularly relevant for the young GCT population. The safety of decreasing the number of surveillance AP-CT scans for CS1 NSGCT patients was demonstrated by the Medical Research

Table 4. Relapse incidence and relapse-free survival

Groups	Total relapses (rate)	Cumulative relapse incidence				
		6 months	1 year	2 years	5 years	7 years
Full cohort ($n = 266$)	70/266 (26%)	28/70 (40%)	47/70 (67%)	56/70 (80%)	65/70 (93%)	69/70 (99%)
SGCT ($n = 131$)	20/131 (15%)	4/20 (20%)	10/20 (50%)	13/20 (65%)	17/20 (85%)	19/20 (95%)
NSGCT						
All ($n = 135$)	50/135 (37%)	24/50 (48%)	37/50 (74%)	43/50 (86%)	48/50 (96%)	50/50 (100%)
RF_0 ($n = 76$)	19/76 (25%)	7/19 (37%)	11/19 (58%)	14/19 (74%)	17/19 (89%)	19/19 (100%)
RF_1 ($n = 41$)	17/41 (41%)	8/17 (47%)	14/17 (82%)	15/17 (88%)	17/17 (100%)	17/17 (100%)
RF_2 ($n = 18$)	14/18 (78%)	9/14 (64%)	12/14 (86%)	14/14 (100%)	14/14 (100%)	14/14 (100%)

SGCT, seminomatous germ-cell tumor; NSGCT, nonseminomatous germ-cell tumor; LVI, lymphovascular invasion; EmbP, embryonal predominance; RF0, LVI− and EmbP−; RF1, LVI or EmbP+; RF2, LVI+ and EmbP+; HR, hazard ratio; CI, confidence interval.

Table 5. Patterns of relapse

Groups	Median time-to-relapse (months)	Risk classification status at relapse			Relapse after first-line chemotherapy	Death secondary to GCT
		Good	Intermediate	Poor		
Full cohort ($n = 266$)	7.5	66/70 (95%)	3/70 (4%)	1/70 (1%)	7/70 (10%)	3/266 (1%)
SGCT ($n = 131$)	11.5	19/20 (95%)	1/20 (5%)	–	2/20 (10%)	1/131 (1%)
NSGCT						
All (50 relapsed)	6.3	47/50 (94%)	2/50 (4%)	1/50 (2%)	5/50 (10%)	2/135 (1%)
RF_0 (19 relapsed)	8.5	17/19 (90%)	1/19 (5%)	1/19 (5%)	2/19 (10%)	1/135 (1%)
RF_1 (17 relapsed)	6.8	17/17 (100%)	–	–	0	0
RF_2 (14 relapsed)	3.8	13/14 (93%)	1/14 (7%)	–	3/14 (21%)	1/135 (1%)

SGCT, seminomatous germ-cell tumor; NSGCT, nonseminomatous germ-cell tumor; GCT, germ-cell tumor; LVI, lymphovascular invasion; EmbP, embryonal predominance; RF0, LVI− and EmbP−; RF1, LVI or EmbP+; RF2, LVI+ and EmbP+; HR, hazard ratio; CI, confidence interval.

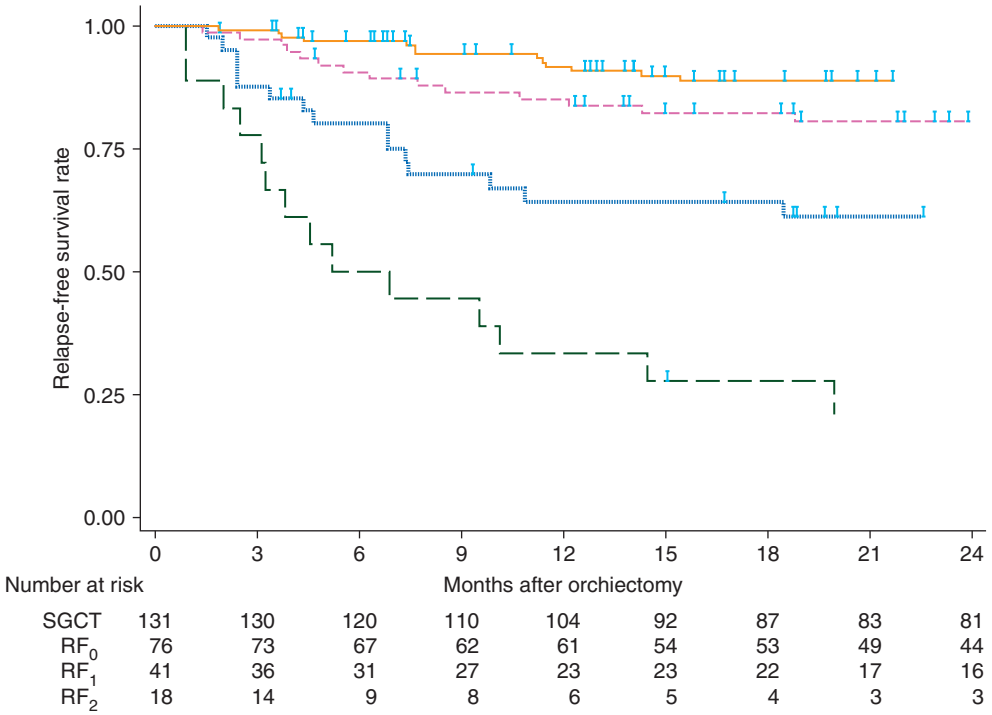

Figure 1. Kaplan–Meier relapse-free survival estimates.

Council (MRC) randomized, controlled trial which randomized 400 patients to CT imaging at either 3 and 12 or 3, 6, 9, 12 and 24 months postorchiectomy [16]. It showed that there was no appreciable increased risk of patients relapsing with intermediate or poor-prognosis disease in the 2 versus 5 scans when patients were also surveyed with frequent plain chest radiographs and blood TMs. The currently employed surveillance regimen leads to significant radiation exposure with as many as 12 AP-CTs within the first 5-year period for NSGCT patients [13]. This number of CT scans typically leads to radiation exposure surpassing the established 5-year 100 mSv cumulative radiation exposure limit. Aiming to minimize the radiation exposure burden associated with active surveillance, we sought to identify low-risk NSGCT patient subsets whose relapse risk would not be affected by less frequent CT scanning.

We selected LVI and EmbP to be the main constituents of the NSGCT risk score given that several prior reports have shown that EmbP and LVI together portend a higher risk of relapse than either one alone, although EmbP's prognostic significance is still actively debated [12, 17, 18]. The EmbP definition avoids the exclusion of patients with substantial embryonal cell cancer which may still lead to an increased risk of recurrence (30%–40%) [19] as the alternate definition (>50% cutoff value) fails to incorporate cases in which the embryonal component predominates such as mixed tumors with multiple tissue subtypes with 40%/30%/30% distributions. Additionally, by assessing EmbP in conjunction with LVI, avoidance of an effect of LVI status upon EmbP status might be avoided [12].

Both the LVI+/LVI− and EmbP+/EmbP− had similar follow-up time intervals, days to first surveillance scan and number of AP-CTs, TMs and visits. Furthermore, the relapse rates obtained in our study are consistent with what has been previously reported for SGCT [20] and NSGCT [6].

We found that the RF score was proportional to relapse rate, incidence rate and cumulative incidence but inversely proportional to RFS and median time-to-relapse. It is of note that we found the RFS for SGCT and NSGCT with neither EmbP nor LVI (RF_0) were similar. Cox regression analysis confirmed that their RFS functions were not statistically different at all time points (including $t_0 = 0$ months). Conditional risk analysis revealed that the absolute and relative relapse probability for all groups was highest during the first 6-month period and progressively decreased thereafter. However, analysis beyond the 1-year time point should be carefully interpreted due to the small sample sizes (particularly on the RF_1/RF_2) and the resulting loss of statistical power.

Recent work by Kollsmannsberger et al. suggests the plausibility of optimizing surveillance schedules by risk-stratifying patients by LVI status [21]. Our study offers an opportunity to further refine these schemes by showing that EmbP may be predictive of relapse when considered in conjunction with LVI. Although this retrospective study is not intended to change practice, it aims to support a prospective evaluation of these findings along with craniocaudal lymph node assessment, as well as other potential novel pathological/ molecular biomarkers and their influence on relapse occurrence and timing.

In summary, we found that the risk stratification of NSGCT patients into a risk score system based on EmbP and LVI yielded three groups with significantly different RFS functions. The lowest risk group (RF_0) behaved similarly to SGCT in terms of time-to-relapse for all recorded time points, while RF_1 and RF_2 joined them at 12 and 18 months, respectively. Our work supports the notion that the surveillance regimen for NSGCT RF_0 may be optimized to resemble that of SGCT patients. Additionally, it is consistent with Kollmannsberger's study but supports utilizing EmbP and LVI status to further risk-stratify patients in order to optimize surveillance regimens.

acknowledgements

We want to give special thanks to Shawmut Design and Construction's Pan Mass Cycling Team for their financial support.

disclosure

The authors have declared no conflicts of interest.

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Annals of Oncology 26: 1401–1408, 2015
doi:10.1093/annonc/mdv190
Published online 23 April 2015

A randomized phase III trial of oral S-1 plus cisplatin versus docetaxel plus cisplatin in Japanese patients with advanced non-small-cell lung cancer: TCOG0701 CATS trial

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Received 25 December 2014; revised 5 March 2015 and 9 April 2015; accepted 13 April 2015

Background: Platinum-based two-drug combination chemotherapy has been standard of care for patients with advanced nonsmall-cell lung cancer (NSCLC). The primary aim was to compare overall survival (OS) of patients with advanced NSCLC between the two chemotherapy regimens. Secondary end points included progression-free survival (PFS), response, safety, and quality of life (QoL).

Patients and methods: Patients with previously untreated stage IIIB or IV NSCLC, an Eastern Cooperative Oncology Group performance status of 0–1 and adequate organ function were randomized to receive either oral S-1 80 mg/m^2/day on days 1–21 plus cisplatin 60 mg/m^2 on day 8 every 4–5 weeks, or docetaxel 60 mg/m^2 on day 1 plus cisplatin 80 mg/m^2 on day 1 every 3–4 weeks, both up to six cycles.

Results: A total of 608 patients from 66 sites in Japan were randomized to S-1 plus cisplatin ($n = 303$) or docetaxel plus cisplatin ($n = 305$). OS for oral S-1 plus cisplatin was noninferior to docetaxel plus cisplatin [median survival, 16.1 versus

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