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Cruciferous vegetables consumption and the risk of female lung cancer: a prospective study and a meta-analysis

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Background: Epidemiological studies evaluating the association between cruciferous vegetables (CVs) intake and female lung cancer risk have produced inconsistent results.

Patients and methods: This study followed 74 914 Chinese women aged 40–70 years who participated in the Shanghai Women's Health Study. CV intake was assessed through a validated food-frequency questionnaire (FFQ) at baseline and reassessed during follow-up. Hazard ratios (HRs) and 95% confidence interval (CIs) were estimated by using Cox proportional hazards models. Furthermore, we carried out a meta-analysis of all observational studies until December 2011.

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Results: After excluding the first 2 years of follow-up, 417 women developed lung cancer over a mean of 11.1 years of follow-up. An inverse association of borderline statistical significance was observed between CV consumption and female lung cancer risk, with HR for the highest compared with the lowest quartiles of 0.73 (95% CI 0.54–1.00, *P* trend = 0.1607). The association was strengthened in analyses restricting to never smokers, with the corresponding HR of 0.59 (95% CI 0.40–0.87, *P* trend = 0.0510). The finding of an inverse association between CV intake and lung cancer risk in women was supported by our meta-analysis of 10 included studies.
Conclusions: Our study suggests that CV consumption may reduce the risk of lung cancer in women, particularly among never smokers.
Key words: cruciferous vegetable, lung cancer, meta-analysis, prospective study, women

introduction

Lung cancer is the most common cancer worldwide with ~1.6 million newly diagnosed cases and an estimated 1.4 million deaths in 2008 [1]. Tobacco is clearly the dominant risk factor for lung cancer and contributed to 80% of the worldwide lung cancer burden in males and at least 50% in females [1]. In China, some epidemiological studies demonstrated that a high proportion of lung cancer in females may reflect indoor air pollution from unventilated coal-fueled stoves and cooking fumes [2, 3]. Apart from these known risk factors, it is important to identify other factors associated with risk and prevention, such as certain groups of fruits and vegetables, which may also be used for primary prevention of lung cancer [4].

Cruciferous vegetables (CVs), named for their four equal-sized petals in the shape of a 'crucifer' cross, including cabbage, broccoli, cauliflower and other members of the family, contain a variety of anticancer constituents such as glucosinolates, the precursors of isothiocyanates (ITCs) as well as indole-3-carbinol (I3C), both of which may contribute to a reduced risk of lung cancer. Evidence from animal studies has suggested that ITCs hinder lung carcinogenesis mainly through inhibition of tobacco smoke procarcinogens, such as polycyclic aromatic hydrocarbons, by phase I enzymes (e.g. cytochrome P450s) and enhancement of detoxification by phase II enzymes (e.g. glutathione S-transferases, GST) [5, 6]. However, a previous meta-analysis failed to carry out the stratified analysis by gender and did not find any significant association between CV consumption and the risk of cases who never smoked [7].

To further clarify whether CV consumption influences female lung cancer risk, we investigated this association in the Shanghai Women's Health Study (SWHS), which is the first and the largest prospective cohort study in Asia to focus on this topic to date. Moreover, we updated the meta-analysis of Lam et al. [7] by adding the data of females from four observational studies (two prospective and two case–control studies) published after publication in 2007 and the results from this current study.

methods

study population, assessment of dietary and follow-up

The Shanghai Women's Health Study (SWHS) is a population-based, prospective cohort study in urban Shanghai, China. All participants provided a written informed consent. The SWHS was approved by the relevant Institutional Review Boards for human research at all participating institutes. Details of the study design, methods, assessment of dietary, follow-up of cohort, adjustment of confounding factors, and etc. are provided in the supplementary Materials, available at *Annals of Oncology* online.

statistical analysis

All statistical analyses were carried out using SAS software, version 9.2 (SAS Institute, Inc, Cary, NC). All *P* values were calculated using two-sided tests and were considered statistically significant if the *P* value was <0.05.

supplementary material

Methods of cohort study, meta-analysis and any associated references are provided under supplementary Methods, available at *Annals of Oncology* online.

results

the shanghai women's health study

Overall, 417 incident cases of lung cancer occurred over an average follow-up of 11.1 years of observation of the SWHS after excluding the first 2 years of follow-up. Table 1 shows the characteristics of the study population by the quartiles of CV consumption reported in the FFQs. Females with a higher CV consumption tended to have a higher body mass index, have higher total energy consumption, be more physically active and have greater per capita family income. Women with greater CV consumption were also less likely to smoke.

As shown in Table 2, CV consumption was inversely associated with female lung cancer risk comparing the highest with the lowest quartile of consumption in an age-adjusted model (hazard ratio, HR: 0.74; 95% CI 0.56–0.97, *P* trend = 0.1036). After adjustment for potential covariates, the inverse association was slightly attenuated and showed borderline significance (HR: 0.73; 95% CI 0.54–1.00, *P* trend = 0.1607). Additionally, we found a significant protective effect of CV consumption among never smokers (HR: 0.59; 95% CI 0.40–0.87, *P* trend = 0.0510), which also showed a borderline dose-response trend.

Regarding the individual CVs, consumption of Chinese greens, cauliflower and white turnip/radish were inversely associated with female lung cancer risk (Table 2), but significant results were only observed for Chinese greens among never smokers, which also suggested a dose-response trend (HR: 0.63; 95% CI 0.44–0.91, *P* trend = 0.0376).

Table 1. Baseline characteristics of the study population according to quartile of cruciferous vegetable (CV) consumption, the Shanghai Women's Health Study, 1997–2009

Characteristic	Quartiles of CV consumption (g/day)				
	<58.49	58.49–87.27	87.27–122.81	≥122.81	*P* value
No. of participants	18 271	18 269	18 271	18 270	
Mean age at recruitment (standard deviation, SD), y	52.3 (9.4)	51.8 (9.0)	51.5 (8.8)	52.4 (9.0)	<0.0001
Mean body mass index (SD), kg/m^2	23.8 (3.5)	23.9 (3.4)	24.0 (3.4)	24.4 (3.5)	<0.0001
Mean total energy intake (SD), kcal/d	1519.1 (319.6)	1605.3 (318.6)	1674.0 (330.9)	1776.8 (378.8)	<0.0001
Mean physical activity (SD), MET, h/week[a]	101.4 (44.0)	105.3 (44.2)	108.3 (45.0)	111.4 (46.8)	<0.0001
Education level, *n* (%)					
Elementary school or less	4329 (23.2)	3685 (20.2)	3605 (19.7)	4063 (22.2)	0.0637
Middle school	6618 (36.2)	6859 (37.6)	7010 (38.4)	6702 (36.7)	
High school	6581 (36.1)	6884 (37.6)	6830 (37.4)	6624 (36.3)	
College or above	830 (4.5)	837 (4.6)	825 (4.5)	877 (4.8)	
Family income, per person per year[b], *n* (%)					
Low	5370 (29.4)	5000 (27.4)	4812 (26.3)	4982 (27.3)	0.0123
Middle	6858 (37.6)	7010 (38.4)	7242 (39.6)	7294 (39.9)	
High	6038 (33.0)	6251 (34.2)	6215 (34.1)	5993 (32.7)	
Smoking status, *n* (%)					
Never smoker	17 626 (96.5)	17 804 (97.5)	17 824 (97.6)	17 800 (97.4)	<0.0001
Former smoker	101 (0.5)	71 (0.4)	59 (0.3)	66 (0.4)	
Current smoker	544 (3.0)	394 (2.1)	388 (2.1)	403 (2.2)	
Ever drank alcohol, *n* (%)	466 (2.6)	376 (2.1)	393 (2.2)	408 (2.2)	0.0798
Family history of lung cancer, *n* (%)	886 (4.9)	875 (4.8)	884 (4.8)	911 (5.0)	0.5181
Post-menopausal, (%)	9141 (50.0)	8724 (47.8)	8586 (47.0)	9296 (50.7)	0.4664

[a]Physical activity level was measured by metabolic equivalent (MET), h/week/year.
[b]Family income level (low income for <5000 yuan/year; medium income for 5000 to <10 000 yuan/year; and high income for ≥10 000 yuan/year).

meta-analysis

Supplementary Figure S1, available at *Annals of Oncology* online illustrates the study selection process. An overview of the 10 original publications [8–17] which qualified for our meta-analysis (supplementary Tables S1–S3, available at *Annals of Oncology* online). In a pooled analysis of these studies, high CV consumption was associated with a significantly reduced risk of female lung cancer (relative risk, RR: 0.75; 95% CI 0.63–0.89) (supplementary Table S4, available at *Annals of Oncology* online, Figure 1). Moderate heterogeneity was observed ($I^2 = 49.0\%$, $P = 0.033$), but no publication bias was observed either using Begg's test ($P = 0.938$) or visually inspecting the funnel plot (not shown). In subgroup analyses defined by study design, study quality, geographic location, smoking status and adjustment for confounders, CV consumption was inversely associated with the risk of female lung cancer in all subgroups, with no evidence of significant heterogeneity between subgroups in meta-regression analyses (supplementary Table S4, available at *Annals of Oncology* online).

In a sensitivity analysis, we sequentially removed one study at a time and re-analyzed the data to determine whether any one study was influencing the results. The 11 study-specific RRs ranged from a low value of 0.70 (95% CI 0.61–0.80) after omitting the study by Wright et al. [10] to a high value of 0.79 (95% CI 0.67–0.93) after omitting the study by Seow et al. [14], but all showed a significant inverse association. Additionally, we removed two studies [12, 14] in which RRs and 95% CIs were not reported but calculated from raw data and the results (RR: 0.78; 95% CI 0.66–0.93) were similar.

discussion

In this study of Chinese women in Shanghai, we observed a borderline statistically significant inverse association between CV consumption and the incidence of lung cancer. When our current findings were included in an updated meta-analysis, the inverse association was again observed and statistically significant. In both of our cohort study and the updated meta-analysis, the association between CV consumption and female lung cancer was stronger among never smokers. In our cohort study, the consumption of Chinese greens also showed a significant dose-response trend among never smokers.

When component CVs were considered individually, the consumption of Chinese greens had a significant inverse association with the risk of female lung cancer in never smokers after controlling the potential confounders. However, it is unclear why we found no clear indication for a reduced risk of female lung cancer in subjects with a high consumption of green cabbage and Chinese cabbage. This may be explained in part by the fact that different CVs have different precursors of glucosinolates, which were the major anticarcinogenic properties of CVs [18]. On the other hand, certain cooking methods, including boiling, steaming and microwaving at high power (850 W–900 W), which inactivate myrosinase, catalyze glucosinolates hydrolysis and decrease the bioactivity of anticancer constituents of CV [19, 20], may also play a role in

Table 2. Hazard ratios (HRs) for lung cancer by quartiles of cruciferous vegetables (CVs) in the Shanghai Women's Health Studies, 1997–2009

Dietary intake (g/day)	All participants			Never smokers		
	No. of cases	HR (95% CI)[a]	HR (95% CI)[b]	No. of cases	HR (95% CI)[a]	HR (95% CI)[c]
CV						
<58.59 (58.76)	123	1.00 (ref)	1.00 (ref)	106	1.00 (ref)	1.00 (ref)
<87.37 (87.54)	94	0.81 (0.62–1.06)	0.81 (0.62–1.07)	88	0.88 (0.66–1.16)	0.77 (0.56–1.06)
<122.82 (122.92)	112	0.99 (0.77–1.28)	1.00 (0.76–1.30)	111	1.12 (0.86–1.47)	0.99 (0.73–1.35)
≥122.82 (122.92)	88	0.74 (0.56–0.97)	0.73 (0.54–1.00)	78	0.75 (0.56–1.00)	0.59 (0.40–0.87)
P for trend		0.1036	0.1607		0.2205	0.0510
Chinese greens[d]						
<42.81 (42.92)	113	1.00 (ref)	1.00 (ref)	99	1.00 (ref)	1.00 (ref)
<67.16 (67.24)	105	0.97 (0.74–1.26)	0.98 (0.75–1.27)	97	1.01 (0.77–1.34)	0.90 (0.66–1.23)
<97.09 (97.13)	110	1.05 (0.80–1.36)	1.06 (0.81–1.38)	106	1.14 (0.86–1.50)	0.98 (0.72–1.34)
≥97.09 (97.13)	89	0.79 (0.60–1.04)	0.80 (0.60–1.08)	81	0.81 (0.61–1.09)	0.63 (0.44–0.91)
P for trend		0.1653	0.2540		0.3064	0.0376
Green cabbage[d]						
<1.13 (1.15)	127	1.00 (ref)	1.00 (ref)	112	1.00 (ref)	1.00 (ref)
<3.75 (3.78)	102	0.96 (0.74–1.25)	0.98 (0.75–1.28)	94	1.00 (0.76–1.31)	0.97 (0.70–1.33)
<7.71 (7.75)	90	0.92 (0.70–1.20)	0.95 (0.72–1.26)	82	0.93 (0.70, 1.24)	0.97 (0.69–1.34)
≥7.71 (7.75)	98	1.00 (0.77–1.31)	1.07 (0.81–1.43)	95	1.08 (0.82, 1.43)	1.21 (0.87–1.70)
P for trend		0.8873	0.7348		0.7234	0.3285
Chinese cabbage[d]						
<1.85 (1.86)	102	1.00 (ref)	1.00 (ref)	88	1.00 (ref)	1.00 (ref)
<4.28 (4.28)	118	1.22 (0.94–1.60)	1.25 (0.96–1.63)	112	1.34 (1.01–1.77)	1.40 (1.01–1.93)
<8.99 (8.98)	92	0.94 (0.71–1.24)	0.97 (0.73–1.29)	84	0.99 (0.73–1.33)	1.06 (0.75–1.50)
≥8.99 (8.98)	105	1.04 (0.79–1.36)	1.09 (0.82–1.46)	99	1.13 (0.85–1.51)	1.26 (0.89–1.79)
P for trend		0.7241	0.9736		0.9108	0.5041
Cauliflower[d]						
<0.83 (0.84)	132	1.00 (ref)	1.00 (ref)	116	1.00 (ref)	1.00 (ref)
<2.44 (2.47)	109	0.97 (0.75–1.25)	0.98 (0.76–1.27)	102	1.02 (0.78–1.33)	0.95 (0.70–1.28)
<5.15 (5.17)	94	0.90 (0.69–1.17)	0.92 (0.70–1.21)	87	0.93 (0.70–1.22)	0.83 (0.61–1.15)
≥5.15 (5.17)	82	0.83 (0.63–1.09)	0.86 (0.64–1.16)	78	0.88 (0.66–1.17)	0.74 (0.52–1.06)
P for trend		0.1576	0.2925		0.3033	0.0784
White turnip/radish[d]						
<0.39 (0.40)	119	1.00 (ref)	1.00 (ref)	107	1.00 (ref)	1.00 (ref)
<2.08 (2.10)	104	0.89 (0.68–1.15)	0.89 (0.68–1.16)	93	0.88 (0.67–1.16)	0.84 (0.61–1.15)
<5.61 (5.64)	100	0.86 (0.66–1.12)	0.88 (0.67–1.16)	95	0.90 (0.68–1.18)	0.87 (0.63–1.20)
≥5.61 (5.64)	94	0.78 (0.60–1.03)	0.80 (0.60–1.07)	88	0.81 (0.61–1.07)	0.83 (0.59–1.16)
P for trend		0.0802	0.1459		0.1710	0.3298

[a]Adjusted for age.
[b]Adjusted for age, body mass index, family income level, education level, total energy intake, physical activity, non-CV intake, smoking status, pack-years of smoking.
[c]Adjusted for age, body mass index, family income level, education level, total energy intake, physical activity, non-CV intake, husband's smoking status, pack-years of smoking exposed by husband, exposed to passive smoking in the work place, total years exposed to passive smoking at work.
[d]Further adjusted for other CVs in the table.

these associations. However, only one study [21] has separated CVs into raw or cooked or by cooking method. Furthermore, there is increasing evidence that genetic variants may influence the effects of CV consumption on cancer risk. London et al. [22] first reported the interaction between ITCs derived from CV consumption and variants of glutathione-*S*-transferases among lung cancer cases in Shanghai. Since then several epidemiological studies have supported these gene–diet interactions in lung cancer [23–25]. Future studies should focus on the individual CVs, cooking method and susceptibility genes which may play an important role in the metabolism of CVs.

The significant inverse effect of CV consumption in our meta-analysis, which was not observed in the previous meta-analysis by Lam et al. [7], may be attributed to the additional published research in the past 4 years. Studies by Wright et al. [10], Lam et al. [11], Lim et al. [17] and Lam et al. [16], including a total of 2948 female lung cancer cases and 195 396 non-cases, accounted for over 71% of the participants in the 10 published studies. These additional studies provided a sufficient sample size to detect the putative association between CV consumption and lung cancer risk among females. Moreover, the results of our meta-analysis remained significant after carrying out various sensitivity analyses. The new analyses

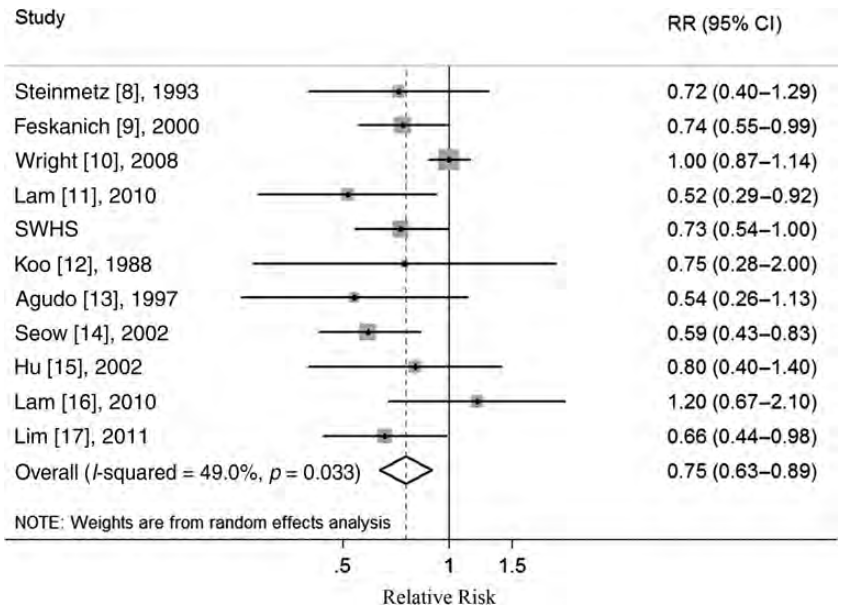

Figure 1. Forest plot (random effects model) of cruciferous vegetables (CVs) consumption and female lung cancer risk in observational studies. Squares indicate study-specific relative risks (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CIs; diamond indicates the summary relative risk estimate with its 95% CI. CI: confidence interval; RR: relative risk; SWHS: the Shanghai Women's Health Study.

conducted here within the SWHS also supported the hypothesis that consumption of CV is inversely associated with female lung cancer risk, especially in never smokers which showed a borderline dose-response trend. Therefore, our results support this inverse association between CV consumption and the risk of female lung cancer.

The inverse association between CV consumption and risk of female lung cancer is biologically plausible. CVs are unique in that they are a good source of glucosinolates, which can be hydrolyzed by the plant enzyme myrosinase into biologically active compounds, including ITC and I3C. Compared with the chemopreventive characteristics of I3C and other phytochemicals and nutrients in CVs, most published research has attributed the multifaceted anticancer properties to ITCs such as the induction of carcinogen-detoxification phase II enzymes, arrest of cell cycle progression and induction of apoptosis [18, 26] Additionally, modulation of metabolism of smoking-related carcinogens by ITCs has been documented in both *in vivo* and *in vitro* studies [6, 27], as well as in humans [28]. ITCs have also been shown to inhibit lung tumorigenesis induced by tobacco-specific carcinogens in animal models [29, 30]. Several studies have also demonstrated that I3C inhibits the transcription of estrogen-responsive genes stimulated by 17β-estradiol [31, 32], which might play a role in the prevention of female lung cancer.

This study has some important strengths. To our knowledge, ours is the first study using a large, prospective cohort study in Asia to consider the association between CV consumption and the risk of female lung cancer. Since this study was based on a prospective design, our findings are unlikely to be explained by recall bias and selection bias. We also carried out sensitivity analyses in our cohort and meta-analysis, and the findings were generally robust. Moreover, our cohort is the only prospective study considering the chronic disease or other cancers studied among the follow-up surveys which may change the dietary habits of the population of SWHS. Since tobacco exposure is such a strong risk factor for lung cancer, we additionally characterized environmental tobacco smoke exposure over the lifetime in the analysis of never smokers of the SWHS. By utilizing information on the passive smoking status at the work place, husband's smoking status and pack-years of smoking, we were better able to potentially adjust for this confounding factor. Furthermore, our cohort included a substantial number of females who were never smokers, accounting for over 97.8% of all participants, which provided sufficient power to detect an association without possible residual confounding by cigarette smoking, as it is well known that cigarette smoking is highly associated with dietary patterns, including fruit and vegetable intakes [33, 34].

Our study also has several limitations. First, our study did not include many current or former smokers. Although the number of people who use tobacco and the number of cigarettes consumed per person have increased substantially in China, the prevalence of smoking among females is not as high as in developed countries [35]. So although Lam et al. [11] and Wright et al. [10] provided evidence for a protective role of CV consumption among current and former smokers, we were unable to test this association. A second limitation was that our study lacked statistical power to stratify by histological subtypes of lung cancer. However, only a case–control study from Japan [36] suggested a significant inverse association between cabbage consumption and small-cell histological type. A third limitation is that both the SWHS and the meta-analysis relied on FFQ data for dietary intake, which may be subject to measurement errors which may attenuate estimates for the dietary-disease associations. Finally, due to different methods and categorizations used to report CV consumption within the studies included in the meta-analysis, we were unable to carry

out a dose-response analysis between CV consumption and female lung cancer risk in our meta-analysis.

In summary, in this large, prospective cohort study and updated meta-analysis, we found convincing evidence for an inverse association between CV consumption and the risk of female lung cancer with stronger associations among never smokers.

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Q-JW, Y-BX designed research; Q-JW, LX and Y-BX conducted research; Q-JW, LX analyzed data; Q-JW wrote the first draft; all authors read, reviewed and approved the final manuscript. Y-BX had primary responsibility for the final content. We would like to thank the participants and the staffs from the Shanghai Women's Health Studies for their contribution to this research.

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disclosure

The authors have declared no conflicts of interest.

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Advanced soft-tissue sarcoma in elderly patients: patterns of care and survival

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Background: There are no data regarding the management of advanced soft-tissue sarcoma (STS) in elderly patients.
Patients and methods: We retrospectively reviewed the charts of patients ≥75 years old diagnosed with metastatic or unresectable STS between 1991 and 2011 in 11 French and American centers.
Results: The study included 361 patients. Of these, 223 patients (62%) received systemic therapy, whereas 123 patients (34%) were managed with best supportive care (BSC) only. Patients who received BSC were more likely to be ≥80 years, with performance status (PS) ≥ 2, Charlson comorbidity score ≥ 10, and metastatic disease. The median progression-free survival of patients treated with systemic therapy was 4 months (95% CI: 2.9–5.1). Thirty-six patients (16%) stopped chemotherapy because of toxicity. Median overall survival (OS) of patients managed with specific therapy was 10.9 months (95% CI: 8.3–13.5) versus 5.3 months (95% CI: 3.6–7.1) for patients managed with BSC ($P = 0.001$). On multivariate analysis, age ≥ 80 years, PS ≥ 2, and number of metastatic sites were the only independent factors associated with OS.
Conclusion: A high proportion of elderly patients with advanced STS were denied chemotherapy. Further efforts are needed to define better the optimal care for fit and unfit elderly patients with STS.
Key words: chemotherapy, elderly, palliative care, sarcoma, soft-tissue sarcoma

introduction

Cancer is a disease of the aging. The number of elderly patients diagnosed with cancer is dramatically increasing and over a third of all cancers are diagnosed in patients >65 years. However, a significant knowledge gap on cancer in older patients exists, making geriatric oncology a critical area of research, indispensable to improve the management of this specific population.

In Europe, the estimated yearly incidence of soft-tissue sarcoma (STS) is 5 cases per 100 000 people [1]. The highest incidence of sarcomas is observed in patients aged between 75 and 84 years with a rate of ∼16% [2]. In the United States, this represents more than 1700 newly diagnosed patients yearly [2]. Compared with their younger counterparts, elderly patients diagnosed with STS present several differences. Indeed, older patients present worse prognosis, with higher grade and larger tumors at presentation [3, 4]. Moreover, recent studies have reported that elderly patients with localized STS may receive less intensive care compared with younger patients [3–7].

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