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Nodal recurrences after stereotactic body radiotherapy for early stage non–small-cell lung cancer

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ABSTRACT

Lobectomy is considered the standard of care for early stage non–small-cell lung cancer. However, for those patients who remain unfit to undergo surgery due to advanced age, poor performance status, comorbidities, poor pulmonary reserve or a combination of these are now treated with stereotactic body radiation therapy (SBRT). Due to its noninvasive nature, lower cost, lower toxicity, reduced recovery time and equivalent efficacy, even medically operable patients are attracted to the option of SBRT despite the lack of level I evidence. Thus, studying the incidence and patterns of recurrence after SBRT help in understanding the magnitude of the problem, risk factors associated with the different patterns of recurrence, and aid in devising strategies to prevent them in future. Nodal recurrences are not uncommon after SBRT and can potentially lead to further seeding for distant metastases and ultimately poor survival. This review is aimed

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at reviewing the published data on the incidence of nodal recurrences after SBRT and compare it to surgery, identify potential risk factors for recurrence, salvage treatment options and prevention strategies.

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Keywords: SBRT; NSCLC; Nodal recurrence; Mediastinal staging

Introduction

Lobectomy with systematic mediastinal lymph node dissection is the standard treatment modality for early stage non–small-cell lung cancer (ES-NSCLC).[1] But patients with advanced age, severe co-morbidities or poor pulmonary reserve at an increased risk of intraoperative or postoperative complications are deemed medically inoperable. For such medically inoperable ES-NSCLC patients or those who refuse surgery, noninvasive stereotactic body radiation therapy (SBRT) is considered a standard treatment option.[2,3] SBRT is a highly precise and conformal type of treatment delivered with high doses per fraction where the adjacent normal tissues get very low doses due to the sharp dose gradient. SBRT provides excellent local control rates and 5-year overall survival close to 40%-45%.[4,5] SBRT is increasing in popularity even among the medically operable ES-NSCLC patients due to the excellent control rates produced with a non-invasive technique. The treatment with SBRT is completed in a few days and has low normal tissue toxicity leading to a much shorter recovery time.[2] These properties of SBRT also make it safe and well tolerated by elderly patients with poor pulmonary reserve allowing them to retain the pretreatment quality of life and activities of daily living.[6]

While SBRT provides excellent local control, the most common pattern of failure is distant metastases (50%) followed by regional failure in the hilar or mediastinal nodes.[7,8] The reasons for this pattern are multifactorial. It has long been held that regional nodal failure may be due to incomplete nodal staging prior to SBRT. However, there are few prospective studies comparing nodal relapses in SBRT with and without prior complete nodal staging. In this review, we aim to discuss the incidence, risk factors for regional nodal recurrence, salvage therapy options and preventive strategies in patients treated with SBRT for ES-NSCLC.

Definitions and patterns of nodal recurrence

Most studies have defined nodal recurrence as any recurrence in the hilar, mediastinal, or supraclavicular nodes. Nodal recurrences reported in the literature were predominantly diagnosed radiologically as appearance of either new nodes suspicious for metastatic involvement or enlargement of the nodes present on the pre-SBRT scan. Since most ES-NSCLC patients are monitored during follow-up using contrast-enhanced computed tomography scan (CECT) of the thorax, there is limited literature on the role of positron emission tomography (PET-CT scan) scan in detection or diagnosis of nodal recurrence. Similarly, even though histologic confirmation of nodal recurrence with biopsy or fine needle aspiration cytology is considered the gold standard for confirmation of metastases, it is sparingly used due to the characteristics of the patient population. These patients are often frail, elderly, have poor effort tolerance, suboptimal lung function or comorbidities, placing them at high risk of adverse outcomes with invasive procedure. Another reason for low rates of histologic verification of nodal recurrence is that many patients suspected to have nodal recurrences are also diagnosed with distant metastases. In such patients with widespread distant metastases, biopsy of the regional nodes is unnecessary. The sensitivity and specificity of a CECT for detecting nodal metastasis range from 55% to 60% and 75% to 80%, respectively.[6,9] Ward et al used different definitions for nodal relapse on the modality used for its diagnosis such as biopsy confirmed mediastinal/hilar node or if biopsy

Table 1
Nodal recurrence in SBRT vs surgical series.

Studies	Number	T stage	IMNS	Nodal recurrence	RRFS (3 years)
Lin et al [23]	Surgery – 246	T1-T2a	Yes	3.7%	94.6%
	SBRT – 70		No	10%	77%
Crabtree et al [12]	Surgery* – 458	T1-T2a	Yes	7%	91%
	SBRT - 151		No	10%	86%
Robinson et al [7]	Surgery – 260	T1-T2a	Yes	17.1%	77.8% (4 y)
	SBRT – 78		No	21.9%	82.9% (4 y)
Grills et al [13]	Wedge – 69	T1-T2	30%	18%	18%
	SBRT – 58		20%	4%	4%
Chang et al [2]	Surgery – 27	T1-T2a	Yes	3.7%	96%
	SBRT – 31		Yes	12.9%	90%

IMNS, invasive mediastinal nodal staging; RRFS, regional recurrence-free survival; SBRT, stereotactic body radiotherapy.

is not feasible then appearance of a new node with 1.0-1.5 cm in short-axis diameter or with standardized uptake value $\geq$3 on PET-CT.[10,11] In 24 patients of isolated regional nodal failure, they showed that majority of nodal relapse occurred in mediastinal nodes rather than the hilar nodes. We found no other published study comparing the incidence of mediastinal vs hilar nodal recurrence post-SBRT.

Incidence of regional nodal recurrence

The reported incidence of nodal recurrence ranges from 5% to 20%.[12-17] It constitutes approximately 30%-40% of all recurrences after SBRT.[18,19] The majority of nodal relapses occur within the first 2 years post-SBRT completion.[20-22] Isolated nodal recurrence is uncommon and ranges from 3% to 5% of all recurrences while majority relapse in combination either with distant or local failure.[10,19] The 3-year regional recurrence-free survival in the SBRT group is approximately 77%-90% vs 67%-92% in the surgery group as reported in the comparative series of surgery and SBRT.[2,12,23] With the increasing popularity and widespread acceptance of SBRT as an alternate treatment modality to surgery for ES-NSCLC, studies focusing on patterns of failure would be critical. Patterns of failure help in generating hypothesis on the need for adjuvant treatment and identification of risk factors for failure help in identifying the subgroups of patients who are likely to benefit from such adjuvant therapies. Failure patterns also guide in selection of salvage therapies and ultimately improve overall survival.

SBRT vs surgery

Till date, there are no completed randomized controlled trials directly comparing SBRT to surgery for ES-NSCLC due to difficulty in accrual of patients. A pooled analysis of 58 patients from the STARS and the ROSEL trials has shown an increased incidence of nodal recurrence in the SBRT group compared to the surgical group (12.9% vs 3.7%). Table 1 lists similar nonrandomized studies comparing nodal recurrence between SBRT and surgical cohort. In all the comparative studies, most of the patients in the SBRT group did not undergo mediastinal staging and were reported to have 10%-20% nodal recurrences post-SBRT. Robinson et al in a retrospective comparison of 338 patients who underwent surgery or SBRT showed upstaging of disease in 32.7% patients after final pathology. Occult nodal metastases were seen in 21.5% patients who went on to receive adjuvant chemotherapy due to the upstaging of the disease. Even in the absence of adjuvant chemotherapy, the SBRT group of patients had a similar 4-year regional recurrence rate of 21.9% compared to 17.1% in the surgery group ($P = 0.91$).[7] There are no studies specifically comparing nodal recurrences between patients treated with surgery vs SBRT where all the patients had undergone complete (invasive) mediastinal staging.

Some speculative studies have indirectly tried to evaluate nodal recurrence rates in patients from the surgical cohort who were also suitable for treatment with SBRT. Robson et al analyzed

Table 2
Nodal recurrence in retrospective studies of SBRT.

Studies	Operability status	Total number	T stage	SBRT dose	PET	Nodal recurrence
RTOG 0236 [4]	Inoperable	55	T1-T2	18 Gy x 3	100%	12.7%
JCOG 0403 [5]	Inoperable	104	T1	12 Gy x 4	Not	7.7
	Operable	65			mandatory	25%
SPACE[14]	Inoperable	49	T1-T2	22 Gy x 3	68%	7%
CHISEL [15]	Inoperable	66	T1-T2a	12 Gy x 4 or 18 Gy x 3	100%	3%
RTOG 0915 [26]	Inoperable	84	T1-T2	34 Gy x 1	100%	10.2%
				12 Gy x 4		4.4%
RTOG 0813 [27]	Inoperable	100	T1-T2	10-12 Gy x 5	100%	11%

PET, positron emission tomography; SBRT, stereotactic body radiotherapy; T, tumor.

Table 3
Nodal recurrence in prospective studies of SBRT.

Studies	Operability status	Total number	T stage	SBRT dose	Mediastinal staging	Nodal recurrence
Ricardi et al [20]	Inoperable	196	T1-T2	48-60 Gy/ 3-8	PET – 75%	14.5% (3 y)
Sun et al [28]	Inoperable	65	T1-T2	12.5 Gy x 4	PET – 100%	10.9% (5 y)
Senthi et al [21]	Inoperable	676	T1-T2	54-60 Gy x 3-8	PET – 100%	12.7% (5 y)
Ward et al [10]	Inoperable	797	T1-T2	NR	NR	6.4%
Lagerwaard et al [29]	Potentially operable	177	T1-T2	60 Gy x 3-8	Not Mandatory	9.7% (3 y)
Lagerwaard et al [22]	Inoperable	167	T1-T2	60 Gy x 3-8	Not Mandatory	9%
	Refused Sx	39				
Baumann et al [30]	Inoperable	57	T1-T2	15 Gy x 3	PET – 32%	5%
Shaverdian et al [11]	Inoperable	147	T1-T2a	18 Gy x 3	NR	13%
				12.5 Gy x 4		
Spratt et al [16]	Inoperable	366	T1-T2a	45-60 × 3-5	PET-100%	17.4% (3 y)
Bradley et al[8]	Inoperable	91	T1-T2	45-54/3-5	PET – 100%	7.7%
Olsen et al [31]	Inoperable	130	T1-T2	18 Gy x 3	PET – 99%	10%
				9 Gy x 5		
Schonewolf et al [32]	Inoperable	236	T1-T2	BED>100Gy	PET – 76.2%	8%
					PET + IMNS – 23.8%	14%
Onishi et al [33]	Operable	87	T1-T2	45-72.5/3-10	NR	14.9% (5 y)

BED, biologically effective dose; IMNS, invasive mediastinal nodal staging; NR, not reported; PET, positron emission tomography; SBRT, stereotactic body radiotherapy; Sx, surgery; T, tumor.

128 patients (89—peripheral and 39—central) who underwent lung resection and showed a 16.4% nodal recurrence rate.[24] Vial et al retrospectively reviewed 246 potentially eligible SBRT patients irrespective of final treatment selected and demonstrated that endobronchial ultrasound-transbronchial needle aspiration changed the nodal stage in 19% of the patients. It upstaged them from N0 to N1 in 3.4% (n = 6/174) and down staged from a clinical N1 to N0 in 50% (n = 36/72) making them suitable for SBRT.[25] This shows that invasive mediastinal staging more often identifies the false positives than the false negatives. This is especially important in patient populations where granulomatous, infective and inflammatory conditions are often encountered.

Nodal recurrence in SBRT series

In both retrospective and prospective SBRT series for ES-NSCLC, the incidence of nodal recurrence is less than 15% in tumors up to 5 cm in size in most of the studies (Tables 2 and 3). In majority of these studies, the mediastinal staging was done with PET-CT alone. Most studies did not specify whether the nodal recurrence was detected in the hilar, mediastinal, supraclavicular, or multiple nodal sites. Both randomized studies (SPACE and CHISEL) comparing SBRT

and conventional fractionation for ES-NSCLC showed nodal recurrence rate of less than 10% in SBRT arm.[14,15] A prospective study by Nagata et al consisting of medically operable and inoperable patients reported nodal recurrence rates of 25% and 7%, respectively. Higher incidence of nodal recurrences in the medically operable patient group may have been due to the longer survival in the medically operable compared to the medically inoperable group (3-year OS 76.5% vs 59.9%).[19]

Impact of nodal recurrence

Nodal recurrence after SBRT is a significant problem as salvage treatment options are limited especially for the patients deemed medically inoperable. Advanced age, poor pulmonary reserve, or multiple comorbidities make most of them ineligible for salvage systemic therapy unless somatic oncogene mutations are present as targeted therapies are tolerated relatively well. The overall survival after nodal recurrence in the absence of salvage treatment is dismal.[10] Nodal metastases can also compress or infiltrate the adjacent critical structures causing airway obstruction, hemoptysis, and swallowing difficulties if left untreated. Thereby, can adversely impact quality of life. In case of isolated nodal failure, it can act as a seeding source for distant metastases. Hence, it is very important to identify the factors responsible for nodal recurrence as it affects the overall outcome of SBRT compared to surgical cohort.

Risk factors for nodal recurrence

The most significant risk factor is the incomplete evaluation of regional lymph nodes as invasive mediastinal staging is not performed routinely. Invasive mediastinal staging can be performed either with mediastinoscopy, endobronchial ultrasound (EBUS) or endoscopic ultrasound (EUS)-guided needle aspiration of mediastinal nodes. The European Society of Thoracic Surgeons guidelines recommend performing regional lymph node evaluation using invasive mediastinal staging before radical lung resections for lung cancer.[34] On the contrary, most of the SBRT guidelines for medically inoperable ES-NSCLC patients do not recommend invasive mediastinal staging prior to SBRT except central and larger tumors.[35] Thus, surgically treated patients have the advantage of knowing the histopathologic nodal status and receive stage-appropriate adjuvant chemotherapy. There is level I evidence to suggest that adjuvant chemotherapy significantly improves disease-free and overall survival in patients with node positive and larger tumors and could also be one of the reasons for relatively inferior survival outcomes with SBRT compared to surgery.[36] In the absence of invasive mediastinal staging before SBRT, there exists a small but definite concern of occult nodal metastases in PET negative patients which could lead to nodal or distant recurrence in the future and lead to poorer survival outcomes.

Unlike local control, nodal recurrence rates did not change with the dose fractionation regimens of SBRT.[37] Some studies that tried to evaluate if nodal recurrence rates varied between medically operable and inoperable patients found no difference if the patients in either groups were staged, treated, and evaluated uniformly on follow-up. This is despite the fact that nearly half of the medically inoperable patients do not survive long enough to experience nodal recurrence (3-year OS was 55%-60%).[5,38] One report suggested that nodal relapses could be lower owing to incidental irradiation of nodal areas close to 20 Gy which will generally be the case in centrally located tumors.[39] Other risk factors for nodal recurrence are determined from large surgical series. These are large tumor size,[22] central tumor location,[24] higher SUVmax of the primary tumor, inadequate radiation dose,[8] and squamous histology.[40] Li et al, in a retrospective evaluation of 189 patients who underwent PET-CT and subsequent lobectomy and systematic LN dissection, demonstrated that size >3 cm and a primary tumor SUVmax >4.3 had the highest risk of occult LN metastases.[41] Similarly, Ye et al also confirmed that the SUVmax >5 of the primary tumor and adenocarcinoma histology were risk factors for presence of nodal metastases.[42]

Even though SUVmax of the primary tumor has been consistently reported as a predictive factor for occult nodal metastases, the cut-off values vary over a wide range.[43-46] Since PET-CT scan is one of the most commonly utilized staging investigations for ES-NSCLC patients and also since its failure to detect nodal metastases is quoted as an important reason for nodal recurrences, a detailed account of its advantages and pitfalls have been provided below.

PET-CT for nodal staging

PET along with CECT is recommended as the standard staging investigation for ES-NSCLC. It detects nodal and distant metastases and upstages approximately 25%-30% patients and thus helps to avoid futile thoracotomies.[47] PET-CT uses metabolic and anatomical information and is superior to CT alone with an approximate sensitivity of 70%-75% and specificity of 85%-95% for detecting metastatic mediastinal nodes.[48,49] However, the sensitivity and specificity decreases with decreasing node size and PET-CT may not be a sensitive investigation for detecting nodes less than a centimeter in size.[50] With a negative predictive value of 85%-90%, PET-CT has the potential to miss nodal metastases in 10%-15% of patients, leading to insufficient therapy to control the disease.[51,52] As stated above earlier, patients with mediastinal nodal metastases receive either neoadjuvant chemotherapy followed by surgery or definitive chemoradiation instead of upfront surgery or SBRT. When SBRT-eligible ES-NSCLC patients are staged with PET-CT alone approximately 10%-15% patients could be harboring occult nodal metastases but do not receive any adjuvant or concurrent systemic therapy and thus are more likely to experience locoregional failure.

Rates of occult nodal metastases in PET negative mediastinum/hila

A designation of PET negative is used for lymph node <1 cm in size with standardized uptake value (SUV) of less than 2.5.[53] Some surgical series have reported 10%-20% chances of having occult micro metastases in mediastinal nodes on histopathology.[41,42] Li et al studied 189 patients staged with PET-CT and deemed negative if SUV <2.5 irrespective of size, and found 18% (34/189) patients with occult nodal metastases. Upstaging from N0 to N1 was seen in 30 patients (15.8%) and N0 to N2 in 14 patients (7.4%), and both N1 and N2 were involved in 10 patients (5.2%).[41] Ghaly et al in their retrospective study of 449 patients with peripheral tumor ≤ 2 cm showed slightly lower rate of occult metastases at 9.6%.[54] Whereas Akthar et al found even lower rate of occult nodal metastases at 7.6% and could be because of patient selection criteria.[52]

Survival with SABR and invasive mediastinal staging

Vial et al in their retrospective comparison between SBRT with prior EBUS (n-81) and SBRT without EBUS (n-88) did not find any difference in locoregional recurrence-free survival and OS.[25] Kennedy et al also similarly compared patients who underwent invasive mediastinal staging ($n=99$) with those who did not ($n=552$) and found no difference in regional recurrence rate and overall survival. Schonewolf et al retrospectively reviewed 236 patents treated with SBRT; 1 group underwent PET-CT alone ($n=180$) while the other underwent PET-CT along with invasive mediastinal staging ($n=56$). This study, surprisingly, showed that the patients in the invasive staging group had 6% nonsignificantly higher nodal recurrence rate at 14% compared to 8% in the PET-CT alone group.[32] Despite higher nodal recurrences the invasive staging group had numerically superior OS (37 vs 47 months, $P = 0.236$) compared to those who underwent staging with PET-CT alone. So, does this mean that all patients who are eligible for SBRT should undergo invasive mediastinal staging? Ideally yes, however, it may not be feasible in patients

with advanced age, poor pulmonary function, and multiple comorbidities as mediastinal staging procedures require some form of anesthesia and many of them are considered unfit for it. This in addition to the availability, waiting time, and willingness of patients to undergo the invasive procedures further add to the challenges.

Patient selection for invasive mediastinal staging

All patients may not require EBUS before SBRT and it may not be worthwhile to do it. In high-risk factors like indeterminate lymph node with size more than 1 cm, tumor size >3 cm, central location with higher SUVmax of the primary tumor. Kennedy et al, in their retrospective study, found higher likelihood of undergoing invasive nodal staging in their group of patients who were young, male, centrally located, and squamous histology.[17] EBUS could be helpful for assessment of mediastinal nodes, especially in patients who are medically operable. Whereas patients in whom the risk of nodal metastases is low, invasive nodal staging might not be required at all. Patients with just ground-glass opacities have minimal risk of LN metastases.[54] Peripheral tumor ≤2 cm size, pure ground-glass opacities, lepidic pattern on histology and SUVmax <2.5 have less than 10% risk of nodal metastases.[42,54-57] The European Society of Thoracic Surgeons guidelines also do not recommend invasive mediastinal staging for peripheral tumors <3 cm size in PET negative mediastinum. American Society of Clinical Oncology recommends EBUS or mediastinoscopy in tumors >5 cm size, centrally located and close to mediastinal structures.[35]

Treatment of nodal recurrences

Salvage treatment options are limited due to the frailty of the treatment population. Additionally, most patients with nodal recurrences also have distant metastases and require treatment with systemic chemotherapy. Targeted therapy using tyrosine kinase inhibitors is preferred if the patient is found to have driver mutations on the initial or a fresh biopsy from the relapsed site. If programmed death or death ligand (PD-1/PD-L1) receptors are present (>1%), immunotherapy can be useful which is less toxic compared to chemotherapy. Isolated nodal recurrences are less common and seen in <5% patients.[10,17] Salvage radiation therapy has been tried in a few studies with or without chemotherapy with reasonable control rates, as noted below. Conventionally fractionated radiation therapy is commonly used to treat nodal failures with doses tailored to individual case scenarios. Manabe et al treated 27 patients of isolated hilar/mediastinal recurrences after prior treatment with surgery and SBRT with conventional fractionation to a dose of 60-66 Gy. They reported 58% LC and 14% OS at 5 years for patients with initial SBRT treatment.[58] Ward et al in a retrospective study of 797 patients reported a 3% (24 patients) isolated nodal failure rate and 15 patients received salvage radiation therapy to a dose of 45 Gy in 15 fractions. The 1-year PFS and OS rates were 75% and 73%, respectively, with no grade 3 or higher toxicity. SBRT for isolated hilar and mediastinal nodes is also being explored as one of the potential treatment options especially after gaining experience in safely treating ultracentral tumors. Horne et al performed SBRT in 40 oligorecurrent nodal metastases after definitive therapy (surgery and radiation) with a good local control of 87.7% at 2 years and 7.5% of grade 3 or higher toxicity.[59] Not surprisingly, they also showed that PFS was significantly better for hilar nodes compared to mediastinal nodes. Surgical salvage is the option for patients who initially refuse surgery but later present with resectable local or nodal recurrence.

Preventive strategies for nodal recurrence

Adjuvant chemotherapy use after SBRT is an option; however, the supporting data are very sparse. Its use is limited as ablative treatment is already performed in node negative el-

derly patients with multiple comorbidities. Retrospective data show that adjuvant chemotherapy was usually given to younger patients with larger tumor size. Chen et al reported that adjuvant chemotherapy improved relapse-free survival and overall survival; however, small patient numbers (n = 17) limit us from drawing any strong conclusions.[60] In a retrospective multi-institutional study with larger number of patients (n = 54), Kann et al demonstrated that addition of systemic therapy reduced the regional and distant failure rate compared to SBRT alone (3.1% vs 16.9%, $P = 0.02$).[61] A large National Cancer Database study (n = 12,000) showed significant benefit in OS from SBRT and adjuvant chemotherapy (n = 2690) in node negative tumors ≥4 cm as compared to SBRT alone (n = 9146).[62] It is well known that risk of nodal recurrences increases with increasing tumor size. Another National Cancer Database analysis confirmed improved OS in tumors more than 5 cm with adjuvant chemotherapy.[63] Incidental nodal irradiation in central tumors could also be one of the factors for reduction in nodal irradiation as one study suggested that ipsilateral hilar nodal relapses are fewer, owing to incidental irradiation of nodal areas close to 20 Gy which will generally be the case in central/ultracentral tumors.[39] Careful follow-up imaging every 3 months for the first few years may help in detecting early recurrences that are easier to salvage.

Two ongoing studies are evaluating the role of EBUS prior to SBRT. First, a US study from MD Anderson Cancer Centre is evaluating the additional value of EBUS with PET-CT in 150 participants of ES-NSCLC prior to SBRT.[64] Second, a Canadian study is being performed to compare the accuracy of endobronchial ultrasound-transbronchial needle aspiration and PET-CT for mediastinal lymph nodes before SBRT in 150 patients.[65] Hopefully, these studies will clarify if invasive mediastinal staging using EBUS is of any additional value in preventing nodal recurrence.

Conclusions

SBRT is increasingly being utilized for the treatment of ES-NSCLC. Therefore, patterns of recurrence including the knowledge of nodal recurrences in high-risk patient population will be of utmost importance. Regional nodal recurrences with or without distant metastases are not uncommon. Most of the medically inoperable patients do not undergo invasive mediastinal staging due to their advanced age, comorbidities, or poor pulmonary reserves. The lack of invasive mediastinal staging is hypothesized to be the reason for higher nodal failure rates with SBRT compared to surgery. However, whether invasive mediastinal staging before SBRT will reduce the nodal recurrence rate or lead to an improvement in overall survival needs to be studied prospectively in a randomized manner.

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