Pathology of Soft Tissue Sarcoma

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Key Words

Sarcoma, pathology, genetics, review

Abstract

The evaluation and treatment of soft tissue sarcomas has never been more demanding than it is today. The pathologist plays a central role in this process and is an integral member of the multidisciplinary sarcoma treatment team. This article provides a brief summary of the role of the soft tissue pathologist and includes sections on methods of diagnosis, frozen section, classification of sarcomas, expert consultation, molecular pathology, grading, assessment of treatment response, and tumor banking. (*JNCCN* 2007;5:411–418)

The evaluation and treatment of soft tissue sarcomas is a demanding process that involves all members of the multidisciplinary sarcoma treatment team, including surgical oncology, medical oncology, radiology, nuclear medicine, pathology, and radiation therapy. Traditionally, the role of the pathologist has been to diagnose disease and evaluate the size of tumors and margin status. However, pathologists are increasingly asked to evaluate molecular characteristics of neoplasms for both diagnosis and prognosis and to comment on the efficacy of neoadjuvant therapy. This article discusses the specific aspects of pathology in the treatment of soft tissue sarcomas.

Diagnosis of Soft Tissue Sarcoma

Before diagnosing soft tissue sarcoma, a clinical history must be obtained, including patient age, gender, and lo-

cation and duration of the lesion. Whether the patient has a predisposition syndrome such as type I neurofibromatosis, which predisposes to neurofibromas and malignant peripheral nerve sheath tumors, or has undergone prior radiation therapy or chemotherapy should also be noted. One of the many benefits of treating sarcomas in the multidisciplinary setting is that this information is readily attainable during weekly multidisciplinary conferences, which also help establish useful communication about patient diagnosis and treatment.

Any discussion of diagnosing soft tissue sarcomas must include how the types of biopsy influence diagnosis. Fine needle aspiration (FNA) is convenient for the surgeon and patient. It is efficient for triaging a soft tissue mass into the 3 basic categories of carcinoma or melanoma, hematolymphoid neoplasm, or sarcoma. However, making an accurate primary diagnosis with FNA can be difficult.¹ Core needle biopsy is easier to interpret than FNA because pathologists can see lesion architecture and cytologic characteristics and because these biopsies compare to open or incisional biopsies in diagnostic accuracy.^{2,3} These samples are also easy to obtain and, for many extremity and chest wall lesions, the biopsy can be performed in the surgical oncologist's office rather than the operating room or imaging facilities. For lesions not accessible in the office, image-directed core needle biopsies can be performed by interventional radiologists. Assessing sample adequacy at biopsy is helpful with either FNA or core needle biopsy; if a pathologist is not available at the site, specimens can be transported to the frozen section room for evaluation.

Multiple core needle biopsies may be required for accurate classification of some lesions because of issues of tumor heterogeneity and sampling. Furthermore, obtaining sufficient tissue for tumor banking and research protocols may be difficult. Contrary to common belief, tissue from both FNA and core needle biopsy can be used for cytogenetics and molecular studies. Finally, FNA and core needle biopsies are excellent methods to reliably

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document local or regional recurrence and distant metastasis when a primary diagnosis is known.

A greater amount of tissue can be obtained with open and excisional biopsies than with FNA or core needle biopsy. Furthermore, snap freezing or otherwise preserving tissue for tumor banking or research protocols is easier from open and excisional biopsies. The advent of genetic, gene expression, and proteomic analysis has increased the importance of banking tissue. Because some centers perform neoadjuvant radiation therapy or chemotherapy for intermediate and high-grade sarcomas, banking tumor tissue from the pretreatment biopsy specimen is ideal.

Frozen Sections

Frozen sections are useful in evaluating sarcoma but, like all techniques, have some limitations. Frozen section analysis is useful for identifying lesional tissue. In other words, determining whether the tissue sent for frozen section analysis is neoplastic is usually straightforward for pathologists. Furthermore, after the lesion is identified, triaging the tissue into the 3 basic categories of carcinoma or melanoma, hematolymphoid neoplasm, or sarcoma, all of which can predominantly involve soft tissue, is useful. With a hematolymphoid neoplasm, tissue should be sent for flow cytometry. With a sarcoma, tissue should be sent for cytogenetics, snap frozen for molecular analysis and tissue banking, and placed in electron microscopy fixative. Receiving potential sarcomas in an unfixed state is ideal because once the tissue is fixed, it cannot be cultured to yield cytogenetic data or frozen for molecular analysis or tumor banking. Distinguishing benign or low-grade from intermediate to high-grade sarcomas at frozen section is also reasonable, although occasionally not possible. Expecting a definitive classification at frozen section is unreasonable. Although it may be possible in some cases, classifying soft tissue sarcomas is sufficiently complex that, in many cases, it can be accomplished only after review of permanent sections and use of ancillary tests.

Analyzing margins can be very difficult at frozen section. Although the pathologist is unlikely to identify a few atypical cells that infiltrate normal tissue, identifying a blatantly positive margin is reasonable. However, these margins are usually also obvious macroscopically to the surgeon. Neoadjuvant radiation or chemotherapy makes determining whether

a margin is contaminated by a neoplasm at frozen section especially difficult. In practical terms, if atypical cells are identified at a margin at frozen section, the margin is usually reported as positive. The frozen section room is a useful setting for the surgeon to review gross resection specimens with the pathologist: the specimen can be oriented and examined, and the margins and any other issues or concerns can be discussed.

Classification of Soft Tissue Sarcomas

Classifying soft tissue sarcomas is complicated because of the large number of diagnostic entities: approximately 50 according to the latest edition of the World Health Organization Classification of Bone and Soft Tissue Tumors.⁴ Sarcomas are classified by line of differentiation into tumors of adipose tissue, smooth muscle, skeletal muscle, and peripheral nerve. However, many sarcomas do not have a well-defined line of differentiation (e.g., Ewing sarcoma/primitive neuroepithelial tumor [PNET]). Furthermore, classifying every sarcoma in a precise fashion may not be possible. Therefore, sarcomas may receive a descriptive classification, such as pleomorphic sarcoma, not otherwise specified (formerly classified as pleomorphic malignant fibrous histiocytoma), or undifferentiated small round blue cell tumor.⁴ Multidisciplinary discussion of how best to treat these tumors is important. In general, classification is accomplished by integrating the clinical information and macroscopic appearance with the histologic findings. Because many sarcomas have overlapping histologic appearances, immunohistochemistry is often necessary to refine the classification. A large number of antibodies/antisera allow pathologists to determine the line of differentiation, which in many cases is sufficient to permit classification of histologically ambiguous lesions. However, immunohistochemistry must be used cautiously and experience is very important, because the immunohistochemical profiles of many sarcomas significantly overlap. Moreover, the immunohistochemical findings may vary within groups of sarcomas with the same diagnosis. Cytogenetic/molecular findings are also useful in classifying sarcomas with well-defined cytogenetic aberrations, especially neoplasms that are morphologically atypical or have unusual clinical characteristics (Table 1).⁵⁻⁷ Although electron microscopy can be useful, it has been largely supplanted by immunohistochemistry at most institutions.

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Table 1 Characteristic Cytogenetic and Molecular Alterations in Sarcomas

Profile	Cytogenetic Alterations	Molecular Alterations
Complex Molecular/Cytogenetic Profile		
Angiosarcoma	Complex	
Leiomyosarcoma	Complex with frequent deletion of 1p	
Malignant peripheral nerve sheath tumor	Complex	
Pleomorphic liposarcoma	Complex	
Pleomorphic rhabdomyosarcoma	Complex	
Pleomorphic sarcoma, NOS (malignant fibrous histiocytoma)	Complex	
Neuroblastoma		
Good prognosis	Hyperdiploid, no 1p deletion	
Poor prognosis	1p deletion	
	Double minute chromosomes	N-myc amplification
Simple Molecular/Cytogenetic Profile		
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	PAX3-FOXO1A fusion
	t(1;13)(p36;q14)	PAX7-FOXO1A fusion
Alveolar soft part sarcoma	t(X;17)(p11;q25)	TFE3-ASPL fusion
Embryonal rhabdomyosarcoma	Trisomies 2q, 8 and 20	
		Loss of heterozygosity at 11p15
Clear cell sarcoma	t(12;22)(q13;q12)	EWSR1-ATF1 fusion
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	EWSR1-WT1 fusion
Dermatofibrosarcoma protuberans	Ring form of chromosomes 17 and 22	COL1A1-PDGFB fusion
	t(17;22)(q21;q13)	COL1A1-PDGFB fusion
Endometrial stromal sarcoma	t(7;17)(p15;q21)	JAZF1-JJAZ1 fusion
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	EWSR1-NR4A3 fusion
	t(9;17)(q22;q11)	TAF2N-NR4A3 fusion
	t(9;15)(q22;q21)	TCF12-NR4A3 fusion
Ewing's sarcoma/PNET	t(11;22)(q24;q12)	EWSR1-FLI1 fusion
	t(21;22)(q12;q12)	EWSR1-ERG fusion
	t(2;22)(q33;q12)	EWSR1-FEV fusion
	t(7;22)(p22;q12)	EWSR1-ETV1 fusion
	t(17;22)(q12;q12)	EWSR1-E1AF fusion
	inv(22)(q12;q12)	EWSR1-ZSG
	t(16;21)(p11;q22)	FUS-ERG
Fibrosarcoma, infantile	t(12;15)(p13;q26)	ETV6-NTRK3 fusion
	Trisomies 8, 11, 17, and 20	
Gastrointestinal stromal tumor	Monosomies 14 and 22	
	Deletion of 1p	
		KIT mutation
Inflammatory myofibroblastic tumor	t(1;2)(q22;p23)	TPM3-ALK
	t(2;19)(p23;p13)	TPM4-ALK
	t(2;17)(p23;q23)	CLTC-ALK
	t(2;2)(p23;q13)	RANB2-ALK

Table 1 Continued

Low-grade fibromyxoid sarcoma	t(7;16)(q33;p11)	<i>FUS-CREB3L2</i> fusion
	t(11;16)(p11;p11)	<i>FUS-CREB3L1</i> fusion
Myxoid/round cell liposarcoma	t(12;16)(q13;p11)	<i>FUS-DDIT3</i> fusion
	t(12;22)(q13;q12)	<i>EWSR1-DDIT3</i> fusion
Myxofibrosarcoma (myxoid MFH)	Ring form of chromosome 12	
Rhabdoid tumor	Deletion of 22q	<i>INI1</i> inactivation
Synovial sarcoma		
Biphasic	t(X;18)(p11;q11)	Predominantly <i>SS18-SSX1</i> fusion
Monophasic	t(X;18)(p11;q11)	<i>SYT-SSX1</i> , <i>SS18-SSX2</i> or <i>SS18-SSX4</i> fusion
Well-differentiated liposarcoma	Ring form of chromosome 12	Amplification of <i>mdm2</i>

Consultation

Because of the complexity and rarity of sarcomas, diagnosis can be very difficult for general surgical pathologists in private practice, who rarely encounter such lesions. One study by a well-known sarcoma consultant showed a major discrepancy in 25% of cases submitted for review.⁸ Of the major discrepancies, 45% were benign mesenchymal tumors diagnosed as sarcomas, 23% were sarcomas diagnosed as benign mesenchymal lesions, 20% were nonmesenchymal lesions diagnosed as sarcomas, and 12% involved major grading discrepancies. Many academic surgical pathologists with subspecialty expertise in sarcomas serve as regional, national, and international consultants. General surgical pathologists are recommended to consult with a pathologist with experience in soft tissue sarcomas when dealing with a neoplasm they have never seen before, or only a few times, or lesions with uncharacteristic morphology or unusual clinical scenarios. This is especially important because different sarcomas may have vastly different prognoses and treatment, and it enables the physician to identify benign mimics of sarcoma such as nodular fasciitis.

Molecular Pathology of Sarcomas

Soft tissue sarcomas can be broadly broken down into those with complex molecular/cytogenetic alterations and those with relatively simple molecular/cytogenetic profiles (Table 1).⁹ The molecular/cytogenetic findings are useful in diagnosis.¹⁰ In addition, these findings may help determine prognosis and response to targeted therapies. Scrupulous attention to quality control is critical in molecular tests, and all new tests for diagnosis or prognosis must be validated extensively.

Cytogenetics has been the gold standard for determining characteristic translocations, but the success rate for cytogenetics is only approximately 50%, even in the best laboratories. Furthermore, cytogenetics is not routinely available in many private pathology laboratories. This is not to say that cytogenetics should not be performed, because a cytogenetic profile can be very helpful and is an excellent research tool for finding new genes and pathways involved in the pathogenesis of sarcomas.

Recently, robust DNA probes for fluorescence in situ hybridization (FISH) have become commercially available that facilitate routine FISH on paraffin-embedded sections for several of the more common translocations (Vysis, Downers Grove, IL). These probes use a break-apart strategy, whereby probes flank a gene involved in the translocation. The probes are together on a normal chromosome that has not undergone a rearrangement/translocation, and break apart on the chromosome when a rearrangement occurs (Figure 1). These probes are versatile because they provide a generalized strategy for detecting translocations. Break-apart probes that span the *EWSR1* region are particularly helpful because they can be used to diagnose Ewing sarcoma/PNET (rearrangement of *EWSR1* with any 5 different translocation partners), desmoplastic small round cell tumor (*EWSR1* with *WT1*), extraskeletal myxoid chondrosarcoma (translocation of *EWSR1* with *NR4A3*), clear cell sarcoma (translocation of *EWSR1* with *ATF1*), and a variant of myxoid liposarcoma (translocation of *EWSR1* with *DDIT3*). Other probe sets are commercially available for diagnosing alveolar rhabdomyosarcoma, inflammatory myofibroblastic tumor, low-grade fibromyxoid sarcoma, myxoid liposarcoma, and synovial sarcoma.

Figure 1 **A.** Hematoxylin and eosin–stained section showing a “small round blue cell tumor.” **B.** Fluorescence in situ hybridization in the same neoplasm in panel A with a break-apart probe set, revealing an *EWSR1* region rearrangement characteristic of Ewing sarcoma/PNET. (Image B courtesy of Dr. Raymond Tubbs, Cleveland Clinic, Cleveland, OH).

Because *Mdm2* amplification is seen in well-differentiated liposarcoma, a FISH probe set has been developed to detect amplified *Mdm2*.^{11,12} Amplifications can also be detected using chromogenic in situ hybridization (CISH) probes, as with *HER2* amplification in breast cancer. CISH probes have been developed for use in detecting *Mdm2* amplification in well-differentiated liposarcoma, but are not commercially available.¹² An advantage of these probes is that they can be used with a light microscope, which increases the ease of use because fluorescence is not required.

Reverse transcriptase polymerase chain reaction (RT-PCR) is also used to identify specific chromosomal translocations. However, because of its inherent sensitivity, RT-PCR has been associated with presumed false-positives caused by contamination when used in conjunction with RNA isolated from paraffin-embedded sections. The tendency for false-positives does not seem to be as much of an issue with frozen tissue. Real-time RT-PCR is also being applied to detecting translocations from paraffin and seems to be much less error-prone, with very few false-positives and -negatives.

DNA sequencing is not used routinely to diagnose soft tissue sarcomas. However, *KIT* or platelet-derived growth factor receptor A (*PDGFRA*) mutations are characteristic of gastrointestinal stromal tumor (GIST).¹³ Furthermore, these mutations are important prognostically because imatinib mesylate and sunitinib maleate are small molecule inhibitors that inhibit *KIT*

and *PDGFRA* and have shown considerable efficacy in the treatment of GIST. Evidence shows that GISTs with *KIT* mutations in different exons and those with *PDGFRA* mutations respond differently to imatinib and sunitinib, and therefore genotyping GISTs may eventually become standard care before therapy is administered.

Molecular prognostic factors have been widely studied in sarcomas. Studies have evaluated the prognostic significance of proliferation markers, DNA content, expression of p-glycoprotein associated with multidrug resistance, p53 expression, type of translocation (many translocations are heterogeneous at the molecular level), and the expression of numerous proteins, including cyclin, survivin, telomerase, vascular endothelial growth factor, E-cadherin, beta-catenin, nm23, SKP-2, p27, and CD40.¹⁴ Although some of these markers look promising, molecular studies currently do not seem to be used to determine prognosis in sarcoma. Further studies are warranted to determine the usefulness of molecular factors in determining prognosis.

New techniques that are being used sparingly to diagnose and delineate the pathogenesis of sarcomas include spectral karyotyping (SKY), gene expression analysis, and comparative genomic hybridization. SKY uses a unique set of probes that, in combination, highlight each chromosome with a different color. This technique is very useful for determining the chromosomal components involved in complex karyotypes, and therefore is useful in solving difficult karyotypes. Gene expression arrays provide information on patterns of gene expression in different sarcomas. Although gene expression arrays have shown consistent gene expression patterns in different sarcomas, they have been used only in the research setting. Gene expression arrays have also been helpful in identifying new markers that can be used in diagnosing sarcomas.¹⁵ Through gene array analysis, *DOG1* and *phosphokinase C theta* have been shown to be good markers for GIST,^{16,17} whereas *TLE1* has been shown to be a good marker for synovial sarcoma, especially in the differential diagnosis of malignant peripheral nerve sheath tumor, which rarely expresses *TLE1*.¹⁸ Comparative genomic hybridization is a useful research technique for identifying gains or losses of chromosomes and chromosomal regions. These gains and losses are helpful in pinpointing oncogenes (gain) and tumor suppressors (loss).

Grading

Unfortunately, no generally accepted scheme exists for grading sarcomas.^{19,20} The 2 most widely used soft tissue grading systems are the French Federation of Cancer Centers Sarcoma Group (FNCLCC) and National Cancer Institute (NCI) systems.^{21,22} Both systems have 3 grades and are based on mitotic activity, necrosis, and differentiation, and predict clinical behavior very well. However, in addition to these criteria, the NCI system requires the quantification of cellularity and pleomorphism for certain subtypes of sarcomas, which is subjective. Furthermore, recent data suggest that the FNCLCC system may be slightly better at predicting prognosis than the NCI system.²³ The College of American Pathologists recommended the FNCLCC system in a recent publication.²⁴ Accurate grading requires an adequate sample of tissue. Because determining the grade accurately with core needle biopsy is not always possible, routine grading of sarcomas using core needle biopsy is not recommended.²⁵ Grading should not be attempted in tumors that have been previously treated with neoadjuvant radiation or chemotherapy.

The FNCLCC grade is based on 3 parameters, with each receiving a score: differentiation (1–3), mitotic activity (1–3), and necrosis (0–2). Differentiation score is related to the diagnosis (Table 2). The score is broken down by 1) sarcomas closely resembling normal, adult mesenchymal tissue, 2) sarcomas of certain histologic type, and 3) synovial sarcomas, embryonal sarcomas, undifferentiated sarcomas, and sarcomas of doubtful tumor type. For instance, sarcomas such as Ewing’s sarcoma/PNET and mesenchymal chondrosarcoma are poorly differentiated and always receive a score of 3, whereas leiomyosarcoma can receive a score from 1 to 3, depending on whether the lesion is well-differentiated and resembles normal smooth muscle (score of 1), conventional leiomyosarcoma (score of 2), or poorly differentiated pleomorphic/epithelioid leiomyosarcoma (score of 3). Mitotic activity ranges among 1) 0 to 9 mitoses per 10 high-power fields (HPF), 2) 10 to 19 mitoses per 10 HPFs, and 3) 20 or more mitoses per 10 HPFs. Necrosis is scored as 0 to 2, with 0 indicating no tumor necrosis, 1 indicating less than or equal to 50% tumor necrosis, and 2 indicating more than 50% tumor necrosis. The scores are totaled and the grade is based on the sum of all scores, with grade 1 characterized by a total score of 3 or less, grade 2 characterized by a total score of 4 to 5, and grade 3 characterized by a total score of 6 to 8.

Table 2 Tumor Differentiation Score According to Histologic Type in the Updated Version of the FNCLCC System

Histologic Type	Score
Well-differentiated liposarcoma	1
Myxoid liposarcoma	2
Round-cell liposarcoma	3
Pleomorphic liposarcoma	3
Dedifferentiated liposarcoma	3
Fibrosarcoma	2
Well-differentiated malignant peripheral nerve sheath tumor	1
Conventional malignant peripheral nerve sheath tumor	2
Poorly differentiated malignant peripheral nerve sheath tumor	3
Myxofibrosarcoma (myxoid MFH)	2
Typical storiform/pleomorphic MFH (pleomorphic sarcoma, NOS)	2
Giant-cell and inflammatory MFH (pleomorphic sarcoma, NOS with giant cells or inflammatory cells).	3
Well-differentiated leiomyosarcoma	1
Conventional leiomyosarcoma	2
Poorly differentiated/pleomorphic/epithelioid leiomyosarcoma	3
Biphasic/monophasic synovial sarcoma	3
Poorly differentiated synovial sarcoma	3
Embryonal/alveolar/pleomorphic rhabdomyosarcoma	3
Extraskelatal myxoid chondrosarcoma	2
Mesenchymal chondrosarcoma	3
Extraskelatal osteosarcoma	3
Ewing sarcoma/PNET	3
Alveolar soft part sarcoma	3
Epithelioid sarcoma	3
Malignant rhabdoid tumor	3
Clear-cell sarcoma	3
Undifferentiated sarcoma	3

Abbreviations: MFH, malignant fibrous histiocytoma; PNET, primitive neuroepithelial tumor; NOS, not otherwise specified. Modified from Goillou L, Coindre JM, Bonichon F, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. *J Clin Oncol* 1997;15:350–362.

Investigators have recently suggested that determining Ki-67 proliferative index might be a better measure of proliferation than mitotic index, and that

it might be especially useful in determining grade from core needle biopsy specimens. Further evaluation is necessary to determine whether Ki-67 index improves on the current FNCLCC grading system's method of assessing grade.²⁶

Although the FNCLCC grading system is adequate for most sarcomas, it has limitations. For instance, grading of malignant peripheral nerve sheath tumor with the FNCLCC system does not correlate well with prognosis.²⁷ Furthermore, grading of soft tissue sarcomas can be unreliable to some extent. For instance, some grade 1 leiomyosarcomas are capable of distant metastasis.²⁸

Assessment of Treatment Response

A universally adopted system for measuring the effect of preoperative (neoadjuvant) chemotherapy/radiation therapy in soft tissue tumors has not been developed. However, because of the increasing use of neoadjuvant chemotherapy and radiation therapy, quantifying these effects is desirable, especially in the research setting. To determine whether neoadjuvant therapy has had any effect, the proportion of fibrosis and necrosis is recommended to be quantified and stated in the final diagnosis.²⁴ However, this is currently purely investigational and not standard practice as it is in quantifying treatment effect in osteosarcoma of bone. Generally, sampling of nonliquified tumor tissue from one cross-section through the longest axis of the tumor is recommended. At least one section of necrotic tumor should be sampled to verify the gross impression of necrosis. Nonsampled necrotic areas should be included in the estimate of necrosis, and the percentage of tumor necrosis should be reported.

Tumor Banking

As mentioned previously, tumor banking has become very important for clinical trials and research into rare tumors such as sarcomas. The authors recommend that all soft tissue sarcomas be banked in institutional tumor banks, whenever possible. Although widely accepted protocols do not exist for banking human tissue, the tumor is recommended to be cut into small (approximately 0.5–0.1 cm³) pieces and frozen as quickly as possible. Normal tissue should also be frozen in the same manner. Furthermore, freezing tumors from biopsy and (assuming enough tissue is present) resection specimens, local recurrences, and distant metastases is

useful because these samples provide unique material to answer various biologic questions. In the future, setting up regional tumor banks for qualified researchers to distribute these tissues would be desirable.

Summary

The pathology of soft tissue sarcoma is a complex arena that presents a bewildering array of diagnostic possibilities for pathologists. Attention to clinical details and histologic, immunohistochemical, molecular, and ultrastructural findings are all useful in determining diagnosis. Recently, the FNCLCC grading system was advocated for determining prognosis. Because we are now in the era of genomic medicine, all sarcomas are recommended to be banked within institutional tumor banks whenever possible so that material is available for research. Experts hope that molecular findings will lead to further advances in diagnosis and treatment.

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