Sarcoma Resection Guided by Intraoperative Indocyanine Green Dye Fluorescence Angiography

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Significance & Hypothesis: Surgical resection with negative margins is foundational in the treatment of soft tissues sarcoma (STS). Intraoperative margin assessment is limited, however, with frozen section providing real-time analysis that is limited by availability of a pathology team. Indocyanine green (ICG) dye is an FDA-approved fluorophore that has been used to guide resection in hepatocellular and breast carcinoma. We hypothesized that ICG fluorescence will be an accurate, real-time, intraoperative margin detector during resection of STS. The purpose of this study was to analyze the utility and accuracy of ICG-guided margin assessment after STS resection.

Innovation: ICG guided resection of STS has been evaluated in a previous study of 18 patients with promising results for intraoperative margin assessment, calling for large sample sizes to better evaluate the utility of ICG in STS resection.

Approach: We performed a prospective clinical study enrolling patients with biopsy-proven STS undergoing surgical resection. Patients presenting with recurrent STS or inadvertent excision were excluded. Included patients received ICG pre-operatively and underwent standard resection followed by ICG fluorescence angiography margin assessment intraoperatively. The fluorescence imager was calibrated to the brightest area of the resected tumor, and margins were classified as positive on angiography if fluorescence was 77% or higher in the operative bed. ICG margin assessment was then compared to frozen and permanent pathology to assess accuracy, sensitivity, and specificity.

Results: A total of 41 patients were included (Table 1). Mean age was 56±14 years, and 51% (N=21) were male. Tumors were high grade in 66% (N=27) and deep in 56% (N=23), and 95% (N=39) of patients received radiotherapy. Mean time from ICG infusion to specimen resection was 3±1 hours, and no patients experienced an adverse reaction. Fluorescence angiography values ranged from 16-98% in resections with positive margins. Maximum fluorescence angiography correlated with area of closest margin in 62% of cases with negative margins and area of positive margin in 100% of cases with positive margins.

With a threshold of 77%, ICG margin assessment demonstrated 73% accuracy with 33% sensitivity, 80% specificity, 22% positive predictive value, and 88% negative predictive value when compared to frozen and permanent pathology. Using a threshold of 60%, sensitivity and negative predictive value improved to 50% and 90% while maintaining similar accuracy (71%), specificity (74%), and positive predictive value (25%). Accuracy was similar in infiltrative histology (undifferentiated pleomorphic sarcoma and myxofibrosarcoma) compared to other histology (74% vs. 75%, p=0.94).

Discussion & Impact: ICG intraoperative margin assessment after STS resection had an accuracy of 73% and specificity of 80% utilizing a fluorescence threshold of 77%, comparable to prior study. Preliminary results demonstrate potential of ICG to assist with intraoperative margin assessment, however further study regarding optimal ICG utilization, fluorescence threshold, anatomic and physiologic limitations, and correlation with local recurrence are needed to assess utility of this emerging technology in STS resection.

Table 1: Tumor and margin characteristics of study cohort

Histology	Grade	Depth	Brightest uptake on fluoresence angiography	Final margin status	Accurate	Closest margin on pathology (cm)	Location of closest or positive margin	Location of brightest margin on fluoresence angiography	Tissue type of brightest margin on fluoresence angiography	LR Status
UPS	3	Deep	9%	R0	Yes	0.3	Deep	Deep	Muscle	LR at 5 months
Myxofibrosarcoma	3	Deep	98%	R1	Yes	Involved	Deep	Deep	Vessels	Negative
Leiomyosarcoma	2	Deep	19%	R0	Yes	0.1	Deep	Deep	Vessels	Negative
MPNST	3	Deep	63%	R1	No	Involved	Inferior	Deep inferior	Muscle	Negative
Myxoliposarcoma	1	Deep	44%	R0	Yes	0.7	Lateral	Superomedial	Fat	Negative
Myxoid sarcoma	1	Superficial	20%	R1	No	Involved	Deep distal	Deep distal	Fascia	Negative
Solitary fibrous tumor	1	Deep	10%	R0	Yes	0.2	Posterior	Deep	Bone	Negative
Myxofibrosarcoma	3	Superficial	41%	R0	Yes	4.1	Anterior	Deep	Joint capsule	Negative
UPS	3	Superficial	81%	R1	Yes	Involved	Deep	Deep	Periosteum	Negative
Myxoid liposarcoma	1	Deep	40%	R0	Yes	1.2	Deep	Deep	Muscle	Negative
Extraskeletal osteosarcoma	3	Superficial	57%	R0	Yes	1.4	Deep	Deep	Muscle	Negative
UPS	3	Superficial	22%	R0	Yes	1.5	Deep	Distal	Skin	Negative
UPS	3	Superficial	53%	R1	No	Involved	Deep	Deep	Fat	Negative
Myxofibrosarcoma	1	Deep	30%	R0	Yes	0.3	Superior	Deep	Muscle	Negative
Malignant tenosynovial giant cell tumor	3	Deep	55%	R0	Yes	0.1	Radial	Deep	Nerve	Negative
Myxofibrosarcoma	3	Deep	25%	R0	Yes	0.5	Medial	Deep	Fascia	Negative
Myxofibrosarcoma	3	Superficial	83%	R0	No	0.7	Deep	Deep	Muscle	Negative
UPS	3	Superficial	200%	R0	No	2	Deep	Deep	Periosteum	Negative
Myxoid liposarcoma	1	Deep	77%	R0	Yes	0.1	Deep	Deep	Muscle	Negative
Myxoid liposarcoma	1	Deep	78%	R0	No	0.2	Deep	Deep	Vessels	Negative
Extraskeletal osteosarcoma	3	Superficial	59%	R0	Yes	0.4	Deep	Deep	Muscle	Negative
UPS	3	Superficial	108%	R0	No	<0.1	Deep	Deep	Periosteum	Negative
Myxoid liposarcoma	1	Deep	58%	R0	Yes	0.3	Inferior	Superficial	Fat	Negative
Dedifferentiated liposarcoma	2	Deep	41%	R0	Yes	0.2	Superficial	Deep	Periosteum	Negative
Extraskeletal myxoid chondrosarcoma	1	Deep	42%	R0	Yes	0.1	Deep, perineural	Deep, periosteum	Bone	Negative
Fibromyxoid sarcoma	1	Deep	38%	R0	Yes	0.1	Deep	Deep	Muscle	Negative
Round cell sarcoma	3	Superficial	146%	R0	No	Involved	Deep	Deep	Fascia	Negative
Rhabdomyosarcoma	2	Superficial	14%	R0	Yes	1.1	Deep	Deep	Fascia	Negative
UPS	3	Deep	16%	R1	No	Involved	Deep	Deep	Ligament	Negative
Myxofibrosarcoma	2	Superficial	37%	R0	Yes	2.8	Deep	Medial	Skin	Negative
Dedifferentiated liposarcoma	3	Deep	41%	R0	Yes	0.1	Deep	Deep	Joint capsule	Negative
Myxofibrosarcoma	3	Superficial	31%	R0	Yes	0.2	Deep	Deep	Nerve	Negative
UPS	3	Deep	50%	R0	Yes	0.3	Superior	Deep	Fat	Negative
UPS	3	Deep	40%	R0	Yes	0.5	Anteromedial	Deep	Muscle	Negative
Fibrosarcoma	3	Superficial	100%	R0	No	1.7	Lateral	Inferior	Fat	Negative
Leiomyosarcoma	3	Deep	10%	R0	Yes	0.2	Deep posterior	Deep posterior	Fat	Negative
UPS	3	Deep	57%	R0	Yes	0.5	Distal	Distal	Muscle	Negative
Leiomyosarcoma	3	Superficial	63%	R0	Yes	0.7	Proximal	Proximal	Fat	Negative
Synovial sarcoma	3	Superficial	140%	R0	No	0.4	Deep	Deep	Synovium	Negative
UPS	3	Deep	40%	R0	Yes	0.3	Posterolateral	Deep	Fascia	Negative
UPS	3	Superficial	47%	R0	Yes	0.2	Deep	Deep	Fascia	Negative

UPS: Undifferentiated pleomorphic sarcoma; MPNST: Malignant peripheral nerve sheath tumor; LR: Local recurrence.