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Comparison of detection sensitivity of near infrared (NIR) surgical imaging systems using a connective tissue phantom model

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Abstract

Many tumors for which fluorescence guided surgery (FGS) has been developed are surface tumors, where direct visualization by the surgeon is straightforward. On the other hand, cancers such as soft-tissue sarcomas, are present at a subsurface level. Resection of these sub-surface tumors is performed using 'wide local excision' where a single, complete mass is removed with an intact zone of normal tissue (~ 1 cm 'margin'). We used a phantom model for sarcoma with near infrared fluorophore IRDye800 CW that defined different tissue properties. We compare the detection sensitivity of two commercially available near infrared (NIR) surgical imaging systems, Solaris (Perkin Elmer) and SPY PHI (Novadaq) using the phantom models of sarcoma. We also determine targeted fluorescence signal on both systems for blinded surgical phantom dissection by a surgeon. The fluorescence intensities are higher for Solaris than for SPY-PHI. On average, the fluorescence increased with an increase in intralipid concentration and decreased with an increase in blood concentration. The depth of imaging was higher for Solaris than for SPY PHI. Using the target values, the surgeon successfully dissected all phantoms using Solaris. Using fat phantoms for SPY PHI, the surgeon cut through four out of the total. Further improvement in FGS will improve cancer recurrence and morbidity.

Keywords

fluorescence guided surgery; indirect visualization; sarcoma; near infrared fluorescence

1. INTRODUCTION

Surgical resection is the main treatment method for many tumors. Despite advances in preoperative imaging, the resection is predominantly based on the ability of the surgeon to identify the tumor using conventional white light imaging. Being unable to excise the entire tumor leads to tumor recurrence and morbidity. Many methods have been developed that

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assist surgeons in locating and excising the tumor. A promising solution is fluorescence guided surgery (FGS) which is more specific, is safer to use, has low cost and provides more direct tumor visualization. For the past decade, FGS primarily used a fluorescent dye indocyanine green (ICG) to image tissue perfusion and vascular function. (1) Increasingly targeted molecular agents are being developed that provide more specificity thereby making it molecular guided surgery in a true sense. While the agent mainly helps in visualization during surgery, this technology can be extrapolated to provide targeted therapy using the same agent simultaneously.

Many tumors for which fluorescence guided surgery has been developed are surface tumors, where direct visualization by the surgeon is straightforward. On the other hand, cancers such as soft-tissue sarcomas which are cancers of the bones, muscles, nerves, and fat and that require complete surgical removal for cure, are present at a subsurface level. Resection of these sub-surface tumors is performed using 'wide local excision' where a single, complete mass is removed with an intact zone of normal tissue (~ 1 cm 'margin'). At present positive margin rates are 22% to 34% for sarcoma which lead to tumor recurrence. (2–3) This has been improved by development in fluorescence guidance of sarcomas but it can be further accelerated by using molecular targets. It is known that sarcoma tumors overexpress epidermal growth factor receptor (EGFR) in 43% to 78% of the cases. (4) ABY-029 is a synthetic anti-epidermal growth factor receptor (EGFR) affibody molecule covalently bound to IRDye 800CW which is fluorescent. It can be used for targeted fluorescent imaging of sarcoma. ABY-029, developed under Good Manufacturing Practice (GMP) production, received eIND (#122681) approval status in 2016. One of the main advantages of ABY-029 is its smaller plasma half-life which makes surgery possible only a few hours after administration. In an ongoing clinical trial (NTC03154411), we are investigating micro dose administration of ABY-029 as an FGS imaging agent in soft-tissue sarcoma patients. However, we require modelling and validation in phantom and animal models to fully develop visualization methodologies. An advanced surgical imaging system must also be selected and tested. At present, there are many US FDA approved systems for near infrared fluorescence guided surgery. (5)

In this paper, we compare the detection sensitivity of two commercially available near infrared (NIR) surgical imaging systems, Solaris (Perkin Elmer) and SPY PHI (Novadaq), in gelatin phantom models of sarcoma. The three types of phantoms investigate the effect of varying tissue types on fluorescence intensity, the effect of tumor and tissue properties on depth of imaging and the effect of volume on observed fluorescence. We also determine targeted fluorescence signal on both systems for blinded surgical phantom dissection by a surgeon.

2. MATERIALS AND METHODS

The preparation of the gelatin phantoms has been well described earlier. (6) We used 10% w/v gelatin phantoms. Gelatin was mixed with boiling distilled water, stirred vigorously while cooling to ~30°C which is when blood and intralipid were added according to the type of the tissue being made. Whole bovine blood (Lampire Biological Laboratories, Inc., Pipersfield, Pennsylvania) and intralipid (Baxter Healthcare Corporation, Deerfield Illinois)

was used. The absorption coefficient of 1% blood and 20 μ M hemoglobin at 800 nm is 0.0004 mm⁻¹. The scattering coefficient of 1% intralipid at 800 nm is 1.0 mm⁻¹. All images were obtained on SPY PHI and the 750 nm channel of Solaris. Detailed analysis of the images has been described in (6).

For imaging well phantoms, sixteen black plastic wells were used, each containing different concentrations of blood and intralipid and same concentration of IReDye 800CW. We used wedge phantoms to determine the effect of tumor and tissue properties on depth of imaging. The inclusion depth varied from 0.5 cm to 3.0 cm. The inclusion diameter varied from 4 mm to 17 mm. An infinite or 3:1 tumor to background ratio was used. Depth of imaging was determined for each condition by taking the natural log of fluorescent values and fitting for intersection with the control.

We also used surgical phantoms to determine the effect of volume on observed fluorescence. The targeted fluorescence signal for dissection was obtained by plotting the measured margin against fluorescence intensity and then fitting for 10 mm target margin.

3. RESULTS AND DISCUSSION

The phantoms were developed to reflect the optical properties of different tissues. Blood was used as an absorbing agent and intralipid was added as a scattering agent in appropriate proportions within the optical range of human connective tissue. In the well phantom set up, the observed fluorescence of IReDye 800 CW varied with different concentrations of intralipid and blood. Figure 1(a) and 1(b) show the images obtained using Solaris and SPY PHI respectively. Figure 1(c) plots for Solaris average fluorescence intensity against amount of intralipid (%) with varying blood concentrations at 77 cm (autofocused height). Minimum values were observed at 5% blood. Figure 1(d) plots for SPY PHI the average fluorescence intensity against amount of intralipid (%) with varying blood concentrations at 60 cm and 30 cm (max and min possible distance). The average fluorescence intensity is higher at 30 cm. The average fluorescence intensities are higher for Solaris than for SPY-PHI. On average, the fluorescence increased with an increase in intralipid concentration. For blood, after an initial increase corresponding to increase in blood concentration, the fluorescence decreased.

Table 1 shows the depth of imaging (in cm) for muscle and fat phantoms as the diameter of the inclusion increases from 4 mm to 17 mm imaged using Solaris and SPY-PHI. For muscle: Using Solaris, the depth of imaging increases from 2.43 cm to 2.68 cm for infinite inclusion to background ratio (IBR) and it increases from 1.10 cm to 2.16 cm for 3:1 IBR. Using SPY-PHI, the depth of imaging increases from 1.07 cm to 1.91 cm for infinite IBR and it increases from 0.09 cm to 0.14 cm for 3:1 IBR. Using SPY-PHI, the depth of imaging increases from 0.64 cm to 1.61 cm for infinite IBR and it increases from 0.53 cm to 0.58 cm for 3:1 IBR. Using SPY-PHI, the depth of imaging increases from 0.64 cm to 1.61 cm for infinite IBR and it increases from 0.53 cm to 0.58 cm for 3:1 IBR. Figure 2(a) and 2(b) depict graphs and images from example wedge phantoms, which were used to calculate the depth of imaging. On average, depth of imaging was proportional to inclusion size for infinite background condition and was higher for Solaris than SPY PHI.

The surgical testing phantoms were used to demonstrate the effect of volume on fluorescence intensity. Figure 3(a) and 3(b) shows the results for muscle and fat phantoms respectively. For both muscle and fat phantoms, minimum fluorescence intensities are observed when the cube is the smallest. Fluorescence decreased with decreasing volume of the phantom. The overall fluorescence value remains almost constant with increasing background fluorescence. The average fluorescence value was higher for fat phantoms in both systems (more difference in Solaris) than muscle phantoms.

The surgical testing phantoms were also used to calculate approximate target fluorescence values at 10 mm margin thickness. Using these values, a blinded surgeon dissected the surgical phantoms with inclusions at random location. The surgeon successfully dissected all phantoms using Solaris. Using fat phantoms for SPY PHI, the surgeon cut through four out of the total. The margin thickness obtained and corresponding fluorescence values are plotted in Figure 4.

4. CONCLUSIONS

Fluorescence guided surgery aims to provide direct visualization of tumor during surgery for wide local excision and in turn to reduce recurrence rates. Development is required especially for tumors which are present at a subsurface level. In this paper, we model and validate the use of fluorescent agent ABY-029 in phantom models to fully develop visualization methodologies. We compare the detection sensitivity of two commercially available near infrared (NIR) surgical imaging systems, Solaris (Perkin Elmer) and SPY PHI (Novadaq). Solaris proves better depth of imaging in general. The fluorescence intensities are higher for Solaris than for SPY-PHI. On average, the fluorescence increased with an increase in intralipid concentration and decreased with an increase in blood concentration. The depth of imaging was higher for Solaris than for SPY PHI. Using the target values, the surgeon successfully dissected all phantoms using Solaris. Using fat phantoms for SPY PHI, the surgeon cut through four out of the total. Further validation through use of animal models is required.

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Figure 1.

Fluorescence of IRDye 800CW in well phantoms with varying bulk tissue properties imaged using (a) Solaris and (b) SPY PHI. The second row shows the average fluorescence intensity for varying levels of intralipid concentration for varying levels of blood concentration on (c) Solaris and (d) SPY PHI.

Figure 2.
Example of determining depth of imaging for muscle and fat phantoms using Solaris and SPY PHI.

Figure 3.
Effect of volume on fluorescence in (a) muscle phantoms and (b) fat phantoms.

Figure 4.

Margin thickness and corresponding fluorescence intensity for surgical dissection phantoms imaged using (a) Solaris and (b) SPY PHI.

Table 1.

Effect of inclusion diameter on depth of imaging (cm)

TISSUE	SYSTEM	TBR	Inclusion Diameter /mm				
			4	6	8	13	17
MUSCLE	Solaris	Infinite	2.43	2.43	2.28	2.51	2.68
		3 : 1	1.10	2.63	1.24	2.47	2.16
	SPY	Infinite	1.07	1.20	1.53	1.90	1.91
		3 : 1	0.09	0.01	0.13	0.18	0.14
FAT	Solaris	Infinite	3.71	3.53	2.46	3.11	17.54
		3 : 1	-	0.72	0.93	1.14	1.38
	SPY	Infinite	0.64	0.90	0.85	0.81	1.16
		3 : 1	0.53	0.53	0.54	0.58	0.58