REFLECTANCE CONFOCAL MICROSCOPY FOR ORAL TONGUE CANCER SURGERY: A FEASIBILITY STUDY
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Introduction: Margin status following surgery for oral tongue squamous cell carcinoma (OTSCC) is an important prognostic factor and frequently affects decisions regarding postoperative management. Frozen section analysis is the only currently available technique to determine whether an adequate resection has been performed. However, this method is influenced by sampling bias, is time consuming, and varies widely from surgeon to surgeon. Reflectance confocal microscopy (RCM) is a well established technology for noninvasive imaging of cellular and architectural detail using the backscatter of laser light. We hypothesize that RCM may offer surgeons a modality to scan the tumor bed in real-time for in vivo detection of residual microscopic tumor. As a prelude to in vivo use, we report an ex vivo feasibility study of RCM for margin assessment in OTSCC.

Methods: Patients undergoing glossectomy at a tertiary cancer center between May 2011 and February 2013 were consented to an IRB approved biospecimen protocol. RCM images were collected of the tumor and adjacent normal tissue immediately following surgery. Pattern recognition was utilized to match RCM images to traditional hematoxylin-eosin (H&E) stained histopathology of the same tissue under the direction of a head and neck pathologist.

Results: Fourteen glossectomy specimens were imaged ex vivo. RCM was performed parallel to the tissue plane (en face) in 9 specimens and perpendicular to the tissue plane in the remaining 5. When analyzing the tumor bed in vivo, RCM would be performed perpendicular to the tissue surface in the same way that traditional H&E sections are processed. Features of healthy mucosa, (such as progressively flattening epithelial migration, a thick optically white lamina propria, and stroma) could be readily distinguished from characteristic features of SCC (such as thinning or disappearance of the lamina propria, inflammation and keratinous swirls in the stroma, non-keratinized cells close to the mucosal surface, and a loss of cell borders and order) as shown in the Figure.

Conclusion: RCM allows real-time ex vivo microscopic optical imaging to distinguish normal tissue from tumor in glossectomy specimens. Our study provides feasibility data for examining the in vivo utility of RCM with a handheld device for intraoperative margin assessment.
S125  ACCURACY AND INTEROBSERVER AGREEMENT OF THE NOVEL PROBE-BASED CONFOCAL LASER ENDOMICROSCOPY FOR THE DETECTION OF HEAD AND NECK NEOPLASIA
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Background: The probe based confocal laser endomicroscopy (pCLE) is gaining popularity for in vivo imaging in the upper gastrointestinal tract. We have described the feasibility of using this technology in differentiating benign from malignant lesions of the head and neck.

Objective: To determine the accuracy and interobserver agreement of pCLE offline images of non-cancer, pre-cancerous and canerous lesions of the head and neck.

Setting: Single Tertiary Referral Center

Methods: In the feasibility study, the senior author formulated image criteria for non-dysplasia: flat, well-organized scale like cells (Figure 1), dysplasia: dark, irregularly thickened and disorganized epithelium (Figure 2), and cancer: crowded dark completely disorganized epitheliumwith leakageof fluorescein (Figure 3). pCLE was performed before lesions were biopsied. 50 offline images and 10 videos of good quality were selected and 3 surgeons and one pathologist were asked to review and categorize the images into the 3 categories above. The overall accuracy of 16 offline pCLE images were compared with histopathology. Sensitivity, specificity and interobserver agreement and accuracy with 95% confidence intervals were determined.

Results: There were 6 non-dysplasia, 7 dysplasia and 11 cancer cases each with multiple images. Sixteen had been biopsied. There was substantial agreement between the four reviewers on the pCLE images and videos (kappa 0.63; 95% CI 0.47-0.80 and k= 0.75; 95% CI 0.48-0.97 respectively). The overall agreement with the final histopathology was substantial for the images and excellent for the video sequences (k=0.69, 95%CI 0.48-0.97 and k=0.86, 95% CI 0.48-0.97 respectively). The sensitivity for the diagnosis of dysplasia vs. non dysplasia, cancer vs. non dysplasia and cancer vs. dysplasia was 80% (95% CI 62-98), 100% and 85.7% (95% CI 73-99) and the specificity was 100% for all three comparison groups.

Conclusions: pCLE for the diagnosis of superficial neoplasia of the head and neck has very high accuracy and reliability. The technology has the potential to decrease sampling error of lesions in the head and neck. This is the first study to test the reliability of this emerging technology in mucosal lesions of the head and neck.
EFFECTIVENESS OF NARROW BAND IMAGING IN THE DETECTION OF RECURRENT OR SECONDARY NEOPLASM IN THE IRRADIATED LARYNX
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Introduction

Narrow Band Imaging (NBI) is considered a significant improvement in the possibility to detect early mucosal lesion of the upper aerodigestive tract.

There is evidence that in patients previously treated by means of radiotherapy (RT) or chemoradiotherapy (CRT), the early detection rate of recurrent disease is quite low.

NBI is based on illumination of mucosa with filtered light. Two narrow bands of light (centred around 415 and 540 nm) penetrate into different depths of mucosa and enhance the contrast between capillary loops and surrounding tissue. Neoangiogenesis that is typical for neoplastic lesions leads to changes of vascular pattern of mucosal microvascularity. A well-demarcated area of these changes with “thick brown dots” is typical for preneoplastic and neoplastic lesions.

Follow-up of irradiated patients is usually very demanding because of the side-effects of the radiation and/or chemotherapy such as soft tissue fibrosis, oedema, and inflammation. The aim of this study was to prove whether the videoendoscopy coupled with NBI might help to detect recurrent or secondary tumours in the upper aerodigestive tract.

Material and methods

Sixty six patients previously treated by means of RT or CRT with curative intent were enrolled in the study. All these patients were evaluated during a follow-up of at least 6 months (range 6-48 months). All patients underwent at least 2 evaluation with an interval of at least 3 months between them unless a suspicious lesion was observed during the first follow-up visit and recurrence detected. Patients underwent transnasal flexible videoendoscopy under local anaesthesia. Whenever a suspicious lesion was identified in ambulatory setting its nature was proved histologically. Findings were classified true positive (TP) if the histological analysis demonstrated anything from severe mucosal dysplasia to infiltrative spinocellular cancer. Patients with persistently negative findings were considered true negative (TN). In majority of cases also the rigid endoscopy and investigation WL and NBI HDTV was performed to prove the negativity. Cases were considered false positive (FP) whenever histology did not reveal tumorous tissue at the area marked by the previous videoendoscopy.

Results

The accuracy of identification of TP tumorous changes was very high (92%), so was the sensitivity and specificity (85% and 94%, respectively). Only in three cases the suspicious endoscopic findings were negative for tumorous cells presence and those patients are considered FP. In two cases the histology showed recurrence of cancer although endoscopy was considered negative. The method has a very high positive predictive (79%) and negative predictive value (96%).
Conclusion

In majority of cases NBI videoendoscopy was proved to be excellent for follow up, in only a very small percentage of patients the recurrence was diagnosed late and lead to the loss of the organ or to the death of a patient. We conclude that NBI videoendoscopy was shown to be superior to any other optical follow-up method we used in the past. Therefore we included NBI videoendoscopy into the follow-up algorithm.

Supported by grant IGA MZ CR NT 11544 and by MH CZ - DRO, University Hospital Motol, Prague, Czech Republic 00064203
**S127 INTRAOPERATIVE CONE-BEAM CT IMAGING FOR HEAD & NECK CANCER SURGERY**

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**BACKGROUND:**

Conventional image-guided surgery systems provide the surgeon with 3D images obtained prior to surgery. In cases involving significant anatomical deformation or tumor excision, these pre-operative images can soon become outdated. The need for precise surgical guidance has motivated the development of imaging systems for intraoperative cone-beam CT (CBCT) imaging. Recently, the UHN Guided Therapeutics (GTx) Program has constructed a new operating room (GTx-OR) specifically designed to support translational research studies in CBCT-guided surgery (Fig.1). This study describes "first in human" clinical trials in head and neck oncology for this novel surgical imaging technology.

**OBJECTIVES**

Primary objective: To evaluate the feasibility and utility of CBCT for head & neck surgical oncology. This includes the assessment of:

1.) Logistical considerations of time, workflow, and compatibility with the OR environment

2.) Image quality under actual clinical conditions

3.) Effect on surgical performance and decision making

Secondary objective: To develop a set of imaging protocols and clinical workflow procedures that enable safe and effective use of CBCT in surgery

**METHODS & Results:**

Patients are recruited under informed consent within the Department of Surgical Oncology. To date, 5 patients have been enrolled in this intraoperative CBCT imaging study to establish "proof of principle" for this technology. A sample case is shown in Fig. 2. Twenty-five patients will be recruited over a wide range of surgical procedures involving cancer resection and anatomical reconstruction in the mandible, maxilla, sinuses, skull base, and temporal bone.

Intraoperative 3D imaging is performed using a CBCT C-Arm mounted on a multi-axis robot (Siemens Zeego). Each patient undergoes at least 3 intraoperative scans: "Planning" - prior to surgical incision; "Post-Excision" - after tumour resection; "Reconstruction" - after surgical reconstruction. An IV contrast injection is used to enhance soft-tissue visibility in CBCT. As CBCT imaging is lower dose than conventional CT, the total accumulated x-ray dose from all scans over the course of the procedure will be kept less than that of one diagnostic CT scan.
The effect of intraoperative imaging and surgical guidance on logistical considerations of time, workflow, and compatibility with the OR environment will be evaluated through the use of in-room audio/video recordings, human factors engineering methods, and expert feedback questionnaires obtained from the surgeons, nurses, and anesthetists involved in each case.

The performance evaluation of the CBCT imaging system will include both quantitative physics-based metrics (e.g., contrast-to-noise ratio, spatial resolution) and surgeon questionnaire-based feedback (e.g., NASA Task Load Index). These results are directly compared to data from our previous prototype CBCT system and conventional diagnostic CT systems.

CONCLUSIONS:

Intraoperative CBCT is feasible during major head and neck surgery with acceptable workflow interruptions and image quality for guidance of cancer ablation and reconstruction procedures. Operations with significant bone ablation and/or reconstruction involving complex 3D anatomical structures are likely to benefit from the updated imaging. The imaging protocols, clinical feedback, and surgical performance metrics resulting from this clinical study will be an essential stepping stone towards more extensive clinical studies involving quantitative assessments of tumour margins and patient outcomes.

Fig. 1. (a) Picture of the GTx-OR at Toronto General Hospital (UHN), including the cone-beam CT C-Arm mounted on a multi-axis robotic control stand (Siemens Zeego) and a dual-source, dual-energy CT scanner (Siemens FLASH).
Figure 2. (a) Intraoperative CBCT image acquisition (~5 sec orbit). (b) Surgical field following resection of sarcoma infiltrating head and neck. (c) Fusion of pre-operative MRI with intraoperative CBCT illustrating region of tumour resection.
S128 PH SENSITIVE NANOPROBE-GUIDED SURGICAL RESECTION OF HEAD AND NECK SQUAMOUS CELL CANCER

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Surgical resection is a cornerstone of therapy for patients with solid cancers, including head and neck squamous cell carcinoma (HNSCC). Obtaining tumor-free surgical margins is an important determinant of disease-free survival and minimizing removal of normal tissue is critical to maximize post-operative function, which in the head and neck region includes speech and swallowing. Achieving these surgical goals requires an ability to distinguish normal tissue from tumor tissue. While pre-operative radiographic imaging can guide resection of the primary tumor, the surgeon still relies upon experience, visual cues and palpation to determine the boundaries of the resection. Even when intraoperative histologic analysis of margins is performed by a pathologist, positive, tumor involved margins, occur. Conversely overestimation of the tumor size often leads to the unnecessary removal of normal tissues as surgical margins compromising speech and swallowing. Recently, we established a series of ultra-pH sensitive (UPS) nanoprobes with tunable, exponential fluorescence activation upon encountering subtle, decreases in physiologically relevant pH. We identified the acidic extracellular tumor microenvironment from aerobic glycolysis, a ubiquitous cancer hallmark, as a general strategy to achieve broad detection of a variety of tumors. The activation of the nanoprobes is achieved through dissociation of the micellar nanoprobe into its component fluorescent dye conjugated polymers, allowing nanoprobes activated in the primary tumor to be detected. We have adopted the UPS design to indocyanine green (ICG), an FDA-approved near IR dye dye (\(?\text{ex}/?\text{em} = 780/820 \text{ nm}\) ). Preliminary data show an exquisitely sharp pH response (\(\Delta \text{pH}_{\text{ON/OFF}} 10-90\% = 0.15\)) with a transition pH at 6.9. The nanoprobes are silent in circulation (at blood pH 7.4), then are sharply activated in response to the low extracellular pH (6.5-6.8) in tumors allowing a high tumor to background ratio (>300-fold). Surgical resection in an orthotopic head and neck cancer tumor model in scid mice allowed good visualization of tumors using the clinical Spy Elite® system. Fluorescent guided surgery in these mice led to statistically significant improvement in survival compared to untreated and surgical controls imaged intraoperatively with white light alone.
Fluorescent Surgery Improved Survival

All animals (including perioperative death):

- Imaging-guided: Median survival (Days) 6 (n=10)
- Non-imaging-guided: Median survival (Days) 12.5 (n=8)
- Non-surgery: Median survival (Days) 14 (n=5)

Animals Alive >72 after Surgery

- Imaging-guided: Median survival (Days) 38 (n=6)
- Non-imaging-guided: Median survival (Days) 19.5 (n=5)
- Non-surgery: Median survival (Days) 14 (n=5)

P<0.05
**Purpose/Objective**

To assess the accuracy of autocontours generated by atlas-based autosegmentation (ABAS) software (Elekta AB) of computed tomography (CT) images in patients with head and neck cancer (HNC).

**Materials and Methods**

Sixteen patients who had completed primary intensity modulated radiotherapy (IMRT) with or without chemotherapy for HNC and who had required replanning of IMRT during treatment were identified retrospectively from a clinical database. The tumour sub-sites included oral cavity (6), oropharynx (3), larynx (2), nasopharynx (1), hypopharynx (1), sinus (1), thyroid/parathyroid (1), unknown primary (1). Original planning CT (CT1) and rescan planning CT (CT2) with associated structure sets were reviewed for the analysis. Structure sets for both CT1 and CT2 for each patient had been delineated manually by experienced clinical oncologists specialising in the management of HNC. For each patient, ABAS was used to generate a new ABAS-delineated structure set on the rescan CT (CT2), using the clinician-delineated structure set together with the original planning CT (CT1) as an atlas. The following regions of interest (ROI) were included for the analysis - high dose and low dose clinical target volumes (CTV1 and CTV2 respectively) and organs at risk (OARs) including spinal cord, brainstem, parotid glands and larynx.

Surrey Heuristic Engine for Radiotherapy, Radiobiology and Imaging (SHERRI) software was used to perform volumetric and morphometric comparisons between the clinician-delineated and the ABAS-delineated structure sets on the rescan CT2. Conformity was quantified in terms of Jaccard conformity index (JCI), mean distance to conformity over- or under-contoured (MDC(O) or MDC(U), respectively) and shift in centre of mass (SCM).
Results

When using CT1 structure sets as an atlas, ABAS generated auto-Contours for CT2 with moderate levels of conformity when compared to those manually contoured by an experienced clinician. On analysis the larynx recorded the largest MDC, undercontouring by 1.97mm. Clinical evaluation of ABAS generated contours by an experienced clinician had 99.1% of auto-contours deemed acceptable with minor modifications. The average time taken by ABAS to auto-contour an entire structure set for each subject was 8 minutes.

Conclusions
1) Atlas based auto-segmentation software (ABAS) (Elekta) can be used to generate clinically relevant radiotherapy volumes with moderate levels of conformity with those manually delineated by an experienced clinician.

2) ABAS could potentially be used to reduce clinician time in re-contouring radiotherapy target volumes and OARs for patients who require replanning of IMRT during treatment. This in turn may provide more time for IMRT plan optimisation to be performed.

3) ABAS generates auto-contours which are clinically acceptable however editing of the contours is required in order to ensure clinical accuracy of delineation.
**S130 QUANTITATIVE EVALUATION OF 89ZR-LABELLED CETUXIMAB ON PET/CT IMAGING: INTRA- AND INTERPATIENT HETEROGENEITY**

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**Purpose/Objective**

Combined treatment with the epidermal growth factor receptor (EGFR) antibody Cetuximab and radiotherapy, shows enhanced tumour response in patients with squamous cell carcinoma of the head and neck (SCCHN). However, Cetuximab is expensive, has side effects and response differs between patients. It is therefore necessary to select patients that are sensitive to the drug, unfortunately EGFR expression on immunohistochemistry is not a reliable tool. We hypothesized that response to Cetuximab is related to EGFR expression and accessibility of the drug to the tumour. In this study we labelled Cetuximab to the long-life Zirconium-89 tracer and evaluate its biodistribution in a series of SCCHN patients using PET/CT imaging.

**Material/methods**

Ten patients with stage III-IV SCCHN, included in the multi-centric ARTFORCE Head and Neck trial (NCT01504815), received a 400 mg/m2 Cetuximab loading dose plus 10 mg (60 MBq) 89Zr-labelled Cetuximab one week before radiotherapy treatment. At two time points before start of radiotherapy, at day 4 and day 7 post-injection of the 89Zr-Cetuximab tracer, PET/CT scans were acquired. The planning CT scans were rigidly registered to the 89Zr-Cetuximab PET/CT scans and gross tumour volume (GTV) delineation was copied from planning CT to 89Zr-Cetuximab dataset. 89Zr-Cetuximab uptake was quantified using standardized uptake values (SUV). Besides a visual analysis of the images, also a quantitative analysis using maximum, mean and peak SUV (SUVmax, SUVmean and SUVpeak, respectively) within the GTV was performed, together with an assessment of (un-specific) average background uptake inside the aortic arch. Tumour-to-background ratios (TBR) were calculated by dividing SUVpeak by background SUVmean and compared between day 4 and 7 post-injection using a Wilcoxon signed rank test.

**Results**

Visual analysis of 10 patients (7 male, 3 female, age range: 45-68y) showed heterogeneous uptake of 89Zr-Cetuximab within the GTV. An example of a 89Zr-Cetuximab PET/CT is shown in Figure 1. Quantification of SUVmax (mean±1SD) was 3.5±2.4 and 1.8±0.9 for day 4 and day 7 respectively, SUVmean: 1.3±0.5 and 0.7±0.3, and SUVpeak: 2.3±1.1 and 1.3±0.6. TBR increased significantly from day 4 (1.4±0.6, range 0.8-2.4) to day 7 (2.4±1.3, range 1.2-5.3), p=0.007. In 4 patients a TBR > 1.4 was observed on the scan of day 4 increasing to 8 patients with a TBR > 1.4 on the scan of day 7.
Conclusion

Uptake of 89Zr-Cetuximab is visually heterogeneous and uptake differs in this group of SCCHN patients. Quantification shows higher tumour-to-background uptake levels of tracer and drug distribution for scans acquired on day 7 than on day 4 post-injection. On the scans of day 7 post-injection, 8 out of 10 patients had significant tumour uptake (defined as TBR > 1.4).
IMAGE VALIDATION IN LARYNGEAL/ HYPOPHARYNGEAL CANCER: IMPROVING TUMOR DELINEATION WITH MRI.
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Introduction:
In radiotherapy the weakest link in accuracy is the large interobserver variation when determining the gross target volume (GTV). Several imaging modalities are used to determine the GTV, of which MRI has superior soft tissue contrast compared to CT and might be more suitable to discriminate between tumor and normal tissue. In our study we aim for improved accuracy of the GTV delineation using MRI in laryngeal/ hypopharyngeal cancer.

Methods and materials:
In 20 patients with squamous cell cancer of the larynx (11) or hypopharynx (9), 5 clinical T3 and 15 clinical T4, prior to total laryngectomy (TLE) 1.5-T-MRI scans (T1w, T2w and T1wGd) were performed in the radiotherapy mould. The GTV was delineated on the MRI scans by three experienced H&N specialists. The GTV was delineated by an experienced head and neck pathologist on the whole mount H&E-sections (Figure 1d and 1e). Details on the pathology-imaging registration have been published previously*. To obtain the accuracy of this golden standard, two dedicated head and neck pathologists delineated the GTV on 10 of the 20 (randomly selected) study cases. The MRI scans were delineated twice individually. At first (del1MRI), all tissue showing enhanced signal intensity (SI) on T2w images were encompassed in the GTV. In the second delineation (del2MRI), high SI on T2w images was considered as peritumoral inflammation, and not included in the GTV** (see also figure 1). Finally, a MRI-GTV (del3MRI) was delineated in consensus between the 3 observers. Volume calculations and overlap analysis expressed as generalized conformity index (Clgen) were performed.

Results:
In the ten patients delineated by three pathologists overlap analysis showed a Clgen of 0.87 (SD 0.04). The distance between overlap and encompassing volumes was smaller than 2 mm in 95%. The mean volume on pathology (n=20) was 12.5 cc (range 3.1-43.4), on del1MRI 24.0 cc (9.5 - 72.1), on del2MRI 18.3 cc (6.3 - 59.7), and on del3MRI 17.5 cc (4.9 - 58.7). The mean Clgen of the delineated del1MRI, del2MRI, and del3MRI with pathology improved from 0.37 (0.25-0.47), to 0.45 (0.28-0.60), and to 0.47 (0.29-0.64), respectively.

Conclusions:
Variation in GTV delineation based on H&E TLE sections was very low, showing the high accuracy of pathology as the golden standard. Determination of the GTV of laryngeal/ hypopharyngeal cancer is overestimated by MRI. By adjusting the guidelines (excluding apparent peritumoral inflammation, i.e. higher SI on T2w images than the tumor bulk) the conformity index improved and overestimation of the GTV decreased.


Figure 1: T1w (a), T1wGd (b), T2w MRI (c); pink: del1MRI; blue: del2MRI; d: Whole mount slice TLE; e: delineation by pathologist on H&E coupe.
THE INFLUENCE OF P16 STATUS ON 18F-FDG PET/CT DETECTING THE PRIMARY TUMOR IN PATIENTS WITH CANCER OF UNKNOWN PRIMARY (CUP)

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Background: Previous reports suggested a benefit of metabolic imaging over routine imaging and clinical exam for cancer of unknown primary (CUP). Therefore, 18F-FDG PET/CT imaging in head and neck squamous cell carcinoma (HNSCC) without a known primary has been shown to be crucial for the detection of the primary tumor. The aim was twofold: first, to assess whether there is a difference in detecting the primary associated with human papilloma virus (HPV) over HPV negative tumors, and second, if there is an additional value in the context of treatment de-escalation.

Methods: Between the years 2003 and 2013 a cohort of 78 patients presented with CUP. In 67 patients a 18F-FDG PET/CT scan was added after panendoscopy for the detection of the primary.

Results: In 34 of 67 (51%) patients the primary was found by the addition of a 18F-FDG PET/CT, whereas in 33 of 67 (49%) no primary could be found. Half of the patients were HPV positive (34/67, 51%). In the HPV positive patients, the majority of primary tumors could be detected (20/34, 59%) whereas in the HPV negative patients, only 11 out of 33 (33%) primary tumors have been detected by 18F-FDG PET/CT. The primary tumors of the HPV positive patients were predominantly located in the tonsils (13/20, 65%) whereas the primaries of the HPV negative were mainly found to be located in other anatomic subsides (4/11, 44%) or in the base of tongue (4/11, 44%).

Conclusions: 18F-FDG PET/CT detects a considerable number of unknown primaries independently from the HPV-status. If the cytology or biopsy of the lymph node metastasis show p16 positivity, there is a higher chance 18F-FDG PET/CT will detect the previously unknown primary whereas if the HNSCC is not HPV-associated, the primary is less likely to be detected by metabolic imaging. A reason for this may be the predominant location of the primary for HPV positive patients in the tonsils with the 18F-FDG PET/CT being prone to this specific anatomic subsite. Regarding the novel concept of de-escalated treatment for HPV-associated oropharyngeal SCC, 18F-FDG PET/CT is a valuable initial staging tool in the CUP situation rendering the primary site a surgical option in the context of treatment de-escalation.