

ONCOLOGY

Ultrasound dye-assisted surgery (USDAS): a promising diagnostic and therapeutic tool for the treatment of cancer recurrences in the neck

Ultrasound dye-assisted surgery (USDAS): un promettente strumento diagnostico e terapeutico per il trattamento delle recidive neoplastiche nel collo

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SUMMARY

The evolution of new techniques for cancer surgery has led to important changes in cancer care in recent years. The endpoint of cancer treatment is now to treat the patient with minimum discomfort while respecting quality of life. New techniques, such as mini-invasive surgery, must respect the correct oncological indications, when technically feasible. The surgery for nodal spread or recurrence of disease, after previous surgery on T or T and N for neck cancer, can represent a diagnostic and therapeutic challenge, especially in the neck, which is characterized by small spaces and noble structures. Often lesions become enveloped in scar tissue and can be difficult to visualize during surgery, representing a genuine problem for the surgeon. Ultrasound dye-assisted surgery is a procedure that combines ultra-sound localization of pathological nodes with the use of methylene blue to mark diseased structures to simplify their visualization (and thus removal) in the surgical field. The technique is simple and can be used in surgically and oncologically experienced hands, even in hospitals that do not have sophisticated technology.

KEY WORDS: Ultrasound • Vital dye • Thyroid cancer • Recurrence

RIASSUNTO

L'evoluzione di nuove tecniche chirurgiche per il trattamento delle neoplasie ha determinato negli ultimi anni profondi cambiamenti filosofici nell'approccio alla cura del cancro. Oggi si cerca di effettuare il trattamento che dà il massimo vantaggio in termini oncologici con il minimo effetto collaterale per il paziente, utilizzando sempre più spesso, ove fattibile, tecniche mini-invasive, cercando di salvaguardare il più possibile la qualità di vita del paziente. La chirurgia delle recidive linfonodali o di carcinomi, dopo pregressa chirurgia su T o su T ed N, può rappresentare un'importante sfida sia diagnostica che terapeutica, in particolar modo nel collo, distretto caratterizzato da spazi angusti e da strutture nobili. Spesso la lesione è inglobata nella pregressa cicatrice ed è difficilmente localizzabile in corso d'intervento, rappresentando un vero e proprio problema per il chirurgo che non sempre riesce a individuarle e ad asportarle. L'USDAS è una metodica che servendosi della guida ecografica e dell'uso di un colorante vitale (blu di metilene) rende visivamente identificabile la recidiva facilitandone l'asportazione. La sua semplicità consente un utilizzo, in mani chirurgicamente ed oncologicamente esperte, anche in strutture che non dispongono di sofisticate tecnologie.

PAROLE CHIAVE: *Ecografia • Recidiva • Cancro della tiroide • Colorante vitale.*

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Introduction

Currently, head and neck surgeon has a large therapeutic repertoire for various diseases in the area of the neck. Surgery, radiotherapy and chemotherapy, with various subdivisions, represent first-line treatment of malignant diseases in this district, which is composed of several anatomically and functionally important structures.

With the development of new surgical techniques and treatments, diagnosis has become as challenging as therapy. From this line of reasoning, some approaches to certain

types of tumours have been attempting to join diagnosis and therapy in a single intervention. One of the challenges in head and neck surgery is the anatomical complexity of the cervical region. Composed of fascias that precisely delimit neck spaces, the neck comprises a noble region rich in blood vessels and important nerves. Therefore, understanding the anatomical arrangement of these structures is fundamental to achieving adequate treatment with low morbidity. Given this, it is evident that, diagnostic and therapeutic approaches in a previously treated patient are

of extreme complexity, and carry a high risk of neurovascular damage with substantial functional consequences. Another common problem is that, given the small size of many residual lesions, it can often be very hard to distinguish tumour from scar tissue; as a consequence, some patients are exposed to unsuccessful surgical attempts at excision^{1,2}. Additionally, even though lymph nodes may be removed, the index node seen preoperatively may not be visualized¹. Therefore, the goal of any methodical diagnostic/approach efficacy must be associated with a low rate of complications. Numerous advances in imaging have been made including ultrasound devices, CT and MRI with increasingly fine and precise resolution, in addition to 18-FDG, PET, with an increase in diagnostic accuracy. Preoperative imaging, which may include ultrasound mapping or another type of imaging, is essential for marking the location of abnormal tissue and for planning the approach to second interventions. However, once an incision is made and tissues are dissected, the clear orientation seen preoperatively is usually lost in the scar tissue¹. Our group has developed a technique previously described by Sippel¹ that aims to facilitate diagnosis of patients with questions on cervical follow-up, which also allows treatment of these lesions with a lower complication rate and morbidity.

Ferlito et al.³ have previously reviewed the continuous development of various types of neck dissection from radical neck dissection at the beginning of the 20th century, functional or modified neck dissection developed in the 1950s and 1960s, to the concept of selective neck dissection. All these progresses have brought less invasive procedures with lower rates of morbidity.

Ultrasound dye assisted surgery (USDAS) represents a new frontier in this pathway by adding radiological precision. Therefore, our dilemma has been how to transfer knowledge of early disease, only seen with ultrasound scan, into observable and objective information for the oncologic surgeon.

Material and methods

Between December 2008 and March 2011, 25 patients underwent USDAS at the European Institute of Oncology, Milan. All patients had been previously treated with surgery and/or I-131 therapy or radiotherapy or chemotherapy and had a suspicious preoperative ultrasound for malignancy or lesions that were difficult to access. Some patients were evaluated with additional imaging techniques such as computed tomography, positron emission tomography, magnetic resonance imaging and scintigraphy.

During surgical procedures we had different intent based on the structure or site under examination. The patients presented a wide spectrum of pathological diseases, diffusely spread along the neck, from the parotid region to the subclavicular space and the superior mediastinal area.

Table I shows the clinical characteristics of patients.

All procedures were performed by an experienced radiologist and surgeon. All specialists presented in the operating theatre. Patients were positioned on operating bed and put under general anaesthesia, and the position of the neck was as comfortable as possible for surgeons in order to make the operation easier.

Preoperative ultrasound was performed (Fig. 1). Pathologic nodes were localized and ultrasound images were compared to other images previously made in the outpatient clinic (Fig. 2). The position of the patients during ultrasound was the same as that used for surgery and was critical to find the correct pathologic area.

Once the critical structures to remove were identified, all anatomic coordinates were taken to help orient the surgeon in the incision and surgical management.

Only a few simple instruments are needed to perform USDAS: one 22 gauge spinal needle, an insulin syringe and an ampoule of methylene blue; syringes were loaded first with a 0.1 ml air bubble, and then with 0.01 ml methylene blue (Fig. 3).

After disinfection of the skin with an alcoholic solution, pathologic structures were localized and targeted with a 22 gauge needle under ultrasound guidance. As the needle was inserted into the structure, the guide was taken off, and the syringe containing methylene blue was inserted and the dye injected (Fig. 4). It was important to inject an air bubble just after the dye in order to transfer all the blue dye into the structure.

After injecting the dye, intervention begins and surgeons continue until the dye is found and the lesion removed (Fig. 5).

Preoperative techniques are easy to carry out and only require about 20 minutes before surgical excision of the diseased or suspect structures. All structures were examined histopathologically.

Results

USDAS was performed in 25 patients during a period of less than 3 years in the context of a multidisciplinary approach. There were 20 (80%) women and 5 (20%) men for a female/male ratio of 4:1. The mean age was 46 years (age range, 14-77 years). Twenty patients (80%) presented disease of the thyroid, and of these 15 had papillary carcinoma and 5 had medullary carcinoma. The remaining five cases had parotid acinic adenocarcinoma (n = 1), adeno cystic carcinoma of the submandibular gland (n = 1), Ewing's sarcoma (n = 1) and squamous cell carcinoma (n = 2; 1 from tongue and 1 from supraglottic larynx).

Twenty-four patients had previously undergone surgery associated with either I-131 therapy, radiotherapy or chemotherapy. Exclusive radiochemotherapy was performed in one case of Ewing's sarcoma.

Table I. Features of patients.

Patient	Sex	Age (yr)	Type of initial cancer	Treatment before USDAS	Preoperative ultrasound	Site of disease (or suspected structure)	Histology
1	F	30	PTC	TT+right LND +I131	Suspect for relapse	1 lym V lev and 1 lym III	PTC
2	F	40	AC parotid gland	left superficial parotidectomy	Suspect for relapse	2 deep parotid lym+1 lym IV lev+4 lym V lev left	Acinic AC
3	F	37	PTC	TT+bilateral LND+I131	Suspect for relapse	7 lym IV lev right+central node	PTC
4	F	45	MTC	TT+bilateral LND	Suspect for relapse	3 central right lym+ 3 central left lym	MTC
5	M	62	PTC	TT+LND+2 SLND+alcoholization 2 lymph nodes IV left level	Suspect for relapse	soft tissues, not lymph nodes	PTC
6	F	65	PTC	TT+I131+bilateral LND +toilette thyroid lodge; 2009: TL extended to cervical oesophagus	Suspect for relapse	2 para-oesophageal lym	PTC
7	M	29	PTC	TT+2 I 131+bilateral CND+left LND	Suspect for relapse	1 lym III lev+1 lym III lev	PTC
8	F	55	MTC	TT+bilateral CND+left LND	Suspect for relapse	2 lym III lev left	MTC
9	F	14	PTC	TT+bilateral CND+left LND(III, IV)+I 131	Suspect for relapse	2 lym V lev	PTC
10	F	28	PTC	TT+bilateral CND+I131	Suspect for relapse	2 lym II lev, 2 lym III lev, 2 lym IV lev left	PTC
11	F	49	PTC	right lobectomy+right LND (II-IV)	Suspect for relapse	14 bilateral central lym+4 lym V lev right	PTC
12	F	39	MTC	TT+bilateral CND	Suspect for relapse	3 lym II lev+2 lym III lev+mass infiltrating plexus	MTC
13	F	44	ACC submandibular gland	demolitive surgery	Suspect for relapse	subcutaneous localization at site of previous scar	ACC
14	M	65	MTC	TT+bilateral CND+bilateral LND	Suspect for relapse	11 lym IV-V-supraclavicular left +1 lym posterior border of SCM	MTC
15	F	60	PTC	TT+I 131	Suspect for relapse	1 lym II lev	PTC
16	F	77	SCC mouth	demolitive surgery+bilateral LND	Clinically negative (PET positive)	SCC on the tip of tongue+inflammatory lymph nodal hyperplasia on lym II lev	Benign
17	M	74	SCC larynx	RT+CT+left radical LND	Suspect for relapse	5 lym II-III-IV-V lev left	SCC
18	F	52	SE	CT+RT	Clinically negative (PET positive)	3 lym IIa:follicular iperplasia, non-metastasis	Benign
19	F	34	MTC	TT+bilateral LND+VI level+I131	Suspect for relapse	1 lym II lev and 1 lym III	MTC
20	F	52	PTC	TT+bilateral CND+I131	Suspect for relapse	1 lym IV lev left	PTC
21	M	42	PTC	TT+I131	Suspect for relapse	1 lym II lev+2 lym III lev+1 lym IV lym+4 central lym	PTC
22	F	26	PTC	TT+bilateral CND+bilateral LND+I131	Suspect for relapse	thyroglossus duct nodule+4 lym (Ia left, Ib right, V left, IV right)	PTC
23	F	39	PTC	TT+I131	Suspect for relapse	3 central lym+3 lym IV lev+2 lym IIA lev+3 lym IIB lev	PTC
24	F	63	PTC	TT+bilateral CND+left LND+I131	Suspect for relapse	1 lym III-IV lev left	PTC
25	F	41	PTC	TT+bilateral LND+2 I131+alcoholization lymph node V level left	Doubtful (lymph node previously treated with alcoholization)	8 lym V lev left+lym external jugular vein	Benign

Histology: PTC papillary thyroid carcinoma; MTC medullary thyroid carcinoma; AC adenocarcinoma; ACC adenocystic carcinoma; SCC squamous cell carcinoma; SE Ewing sarcoma; Technical procedure: TT total thyroidectomy; LND lateral neck dissection; CND central neck dissection; I-131 radiiodine therapy; RT radiotherapy; CT chemotherapy.

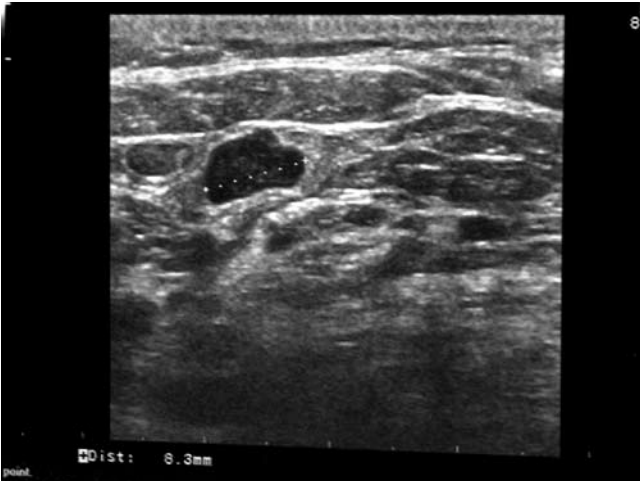


Fig. 1. Preoperative ultrasound image.

Twenty-two of 25 patients had a suspect structures as shown by ultrasound examination.

In two cases, the suspicion of metastatic nodal recurrence was not confirmed by pathological examination. One of these patients previously presented a squamous cell carcinoma of the tongue, and the other a Ewing's sarcoma in the neck. Both patients were evaluated preoperatively with 18-FDG PET that was positive; the final histological examination was negative for the presence of disease.

One patient underwent intervention for a suspect lymph node, previously treated with alcoholization for papillary thyroid carcinoma; the node was dubious by ultrasound, but the patient's desire for pregnancy without fear prompted excision of the lymph node. The histological exam was negative. Eleven cases had fine-needle aspiration (FNA) to confirm diagnosis. All patients used the same quality of methylene blue.

We performed 7 selective neck dissections where only the coloured structures or a single neck dissection level were

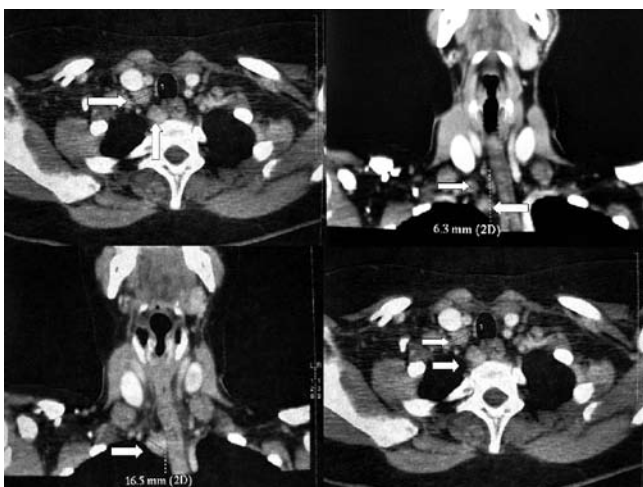


Fig. 2. Papillary carcinoma metastases occurring two years after total thyroidectomy with bilateral neck dissection and 3 treatments with radioiodine I-131. CT showed two localizations in the right neck.

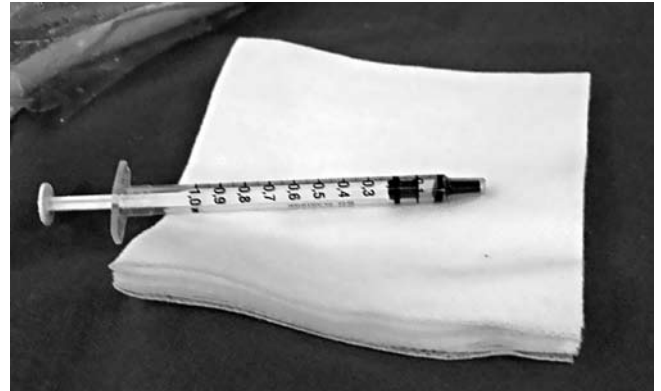


Fig. 3. Syringe with a 0.1 ml air bubble and 0.01 ml methylene blue.



Fig. 4. Patient undergoing ultrasound neck scan under general anaesthesia. Methylene blue dye was injected.



Fig. 5. Surgical specimen.

coloured. The remaining 18 patients underwent extended neck dissection with the excision of two or more neck dissection levels. The dye does not interfere with pathological examination since it is completely washed out during tissue processing.

The injection of 0.01 ml dye eases the determination of pathological structures with no scattering. No case showed neuropathy following the instillation of methylene blue.

All the patients underwent psychiatric and logopaedic evaluation postoperatively. Five patients had postoperative complications that included two hypocalcaemia, two lymphorrhagia and one palsy of the inferior branch of the facial nerve that resolved after six months.

Discussion

Surgical techniques have changed over time and have become increasingly less invasive, reaching the current concept of minimally-invasive surgery. This development has followed increasingly accurate anatomical and biological knowledge, advances in microscopy and ultra-microscopy, and the advent of increasingly sophisticated medical technologies. In particular, there has been a large expansion in radiological techniques such as scintigraphy, CT, MRI and ultrasound. These procedures have led to a detailed study of diseases that only some years ago required so-called “diagnostic surgery”^{4,5}.

The refinement of ultrasound methodologies and increasingly advanced technologies has led to the possibility to recognize disease earlier. Such a trend can be considered explosive in oncology, where early diagnosis is strictly entrusted to radiologists. Experienced specialists with the latest generation of sonographic instruments are able to detect increasingly smaller structures, with a resolution in some cases down to millimetres, especially in tissues previously treated by surgery or other therapies⁶.

In head and neck cancer, ultrasound techniques are increasingly used in diagnosis and follow-up⁷. Ultrasound detection of very small pathological lymph nodes or even submillimetre resolution, has had the consequence that “diagnostic surgery” is almost never performed. While early diagnosis is obviously favoured, this has posed difficulties for the surgeon in finding small structures. In fact, the surgeon does not have the tools to intraoperatively identify small, individual diseased structures.

Over the years, such considerations in head and neck oncology have led us to focus our work as surgeons and radiologists, so that intervention on the neck can be particularly respectful of the anatomic complexity (muscles-blood vessels-nerves). Indeed, small lesions involving blood vessels, nerves or muscles can cause important functional deficits, thus compromising normality and social relations.

Therefore, we considered how ultrasound data could be transformed into information that would be useful for the surgeon. Surgery is usually based on objective, visible and palpable information that depend on four main features of structure measured before and during surgery: shape, volume, consistency and colour. These data are clearly

evident as the size, consistency and colour deviate significantly from normality, but since the ultrasound methods have been improved and the diagnosis of malignancy or recurrence occurs in very early stages, it has become increasingly difficult to identify diseased structures with only minor variations in these 4 features.

Thus, our dilemma has been how to transfer knowledge of early disease, only visible by ultrasound, into observable and objective information for the surgical oncologist.

Our consolidated experience in sentinel nodes has placed us in a position to use, develop and refine an easy and inexpensive “vital dye” technique. For this purpose, we used methylene blue dye which is safe and associated with rare toxicity and very rare allergic reaction. As the blue dye was injected into the ultrasound pathological structure, the coloured fluid spread without altering either anatomical or pathological features. The injected structures become visible to the surgeon for 2-3 hours and target the precise point of intervention. Use of the dye means that the operation is carried out on the basis of visual landmarks. In fact, formations localized by ultrasound, often very small, unique and sometimes localized in previous scars, with changes in shape and volume, cannot be found by palpation.

We called this technique ultrasound-dye-assisted-surgery (USDAS). In the literature many similar methodologies have been described. Kang et al.⁸ used ultrasound-guided tattooing with a charcoal suspension for localization of nonpalpable lesions, but it was difficult to remove during pathologic tissue processing. The technique of hook-needle localization under ultrasound guidance⁹ can be dangerous in cases with multiple lesions or with lesions located near major vessels. Some investigators have^{10,11} injected a radiotracer under ultrasound guidance and then scanned with a probe to localize the area with maximum radioactivity. This method leads to scars and is not visible to the surgeon; it also has to be performed in protective environment, at high cost. Dyes like lymphazurin blue and indigo carmine have been used in other studies with a gradual washout from lesions within 1 hour¹.

USDAS represents a helpful technique to intraoperatively localize small lesions in the neck. It is easy to perform and can precisely localize suspicious lesions, minimizing the effects of a pretreated surgical field and the related risks of damage to neurovascular structures, thus reducing the morbidity of secondary surgical intervention and the risk of surgical failure. In many cases, the procedure can change surgical management by avoiding unnecessary re-intervention and reducing the operation time. We have used USDAS for the cervico-facial district, but it is possible that this technique could be extended to other areas such as breast surgery, general surgery or for treatment of melanoma.

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