RESEARCH ARTICLE

Usefulness of Imaging for Intrathecal Drug Delivery Systems: An update

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Abbreviations:
IDDS Intrathecal Drug Delivery Systems
IT Intrathecal
3D CT Three-dimensional computer tomography

- Abbreviated Title: Intrathecal drug delivery systems imaging in cancer related pain
- Conflicts of interest: Dr Dupoiron received consultant fees from Medtronic
- Financial Disclosures: None
- Number of words in Abstract : 295
- Total Number of words in main text: 3265

Author's individual contribution to the manuscript:
Dr Carvajal, Dr Douillard and Dr Dupoiron participated in conception and design, acquisition of data, analysis and interpretation of data.

Acknowledgements:
The authors would like to thank Aashna Narang for medical editorial assistance

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Abstract

Intrathecal Drug Delivery Systems are invasive pain treatment techniques that require bypassing the blood-brain barrier in order to implant a catheter inside the CSF. Imaging is a key element before and during implantation as well as in the diagnosis of complications.

The understanding of delivery mechanisms has been greatly improved using MRI. Drug diffusion can now be modeled according to infusion level and flow rate for each individual patient. MRI and CT are useful in diagnosing the patient, targeting spinal level, and accurately evaluating implantation concerns or contraindications.

Imaging is a key tool during the implantation of the device. Catheter positioning is essential as the treatment diffusion is limited, and the tip of the catheter must be set behind the spinal cord. Currently, fluoroscopy is the gold standard for catheter placement. Biplane Interventional Imaging and surgical CT scan will soon be able to help with more accurate positioning. An ultrasound-guided technique is helpful to localize a recessed septum in challenging pump refill procedures where pumps are deeply situated.

Imaging is also essential for device malfunction diagnosis. Plain radiology is currently limited as new catheters have a poor opacity, but it remains useful for confirming motor stall of the peristaltic pump and is appropriate for the diagnosis of pump rotation. High-resolution three-dimensional Computer Tomography reconstruction allows accurate control of catheter positioning and the diagnosis of dislodgment, kinking, and breaking. MRI is the most accurate imagery to diagnose spinal cord injuries following implantation or as an adverse effect of IT treatment such as granuloma. Diffusion control requires dynamic imaging which can be performed by TC99 scintigraphy. This allows for the visualization of drug diffusion and velocity. In the near future, novel techniques such as PET- CT scan could be useful for testing the distribution of intrathecal drugs

Keywords: Cancer pain; Chronic Pain; therapy management; Infusions, Spinal; Infusion Pumps, Implantable.

Introduction

The principle of intrathecal analgesia is based on the administration of analgesics to the cerebrospinal fluid (C.S.F.), close to the receptors present in the posterior horn of the spinal cord. The targets for intrathecal treatments are the spinal synapses of afferent nerve fibers Aδ and C found at lamina I, II, and V of the dorsal spinal horn (1, 2). The main advantage of intrathecal drug delivery systems (IDDS) is a considerable decrease in dose administration and a large reduction in side effects. IDDS also allow for the administration of certain analgesics, which could not be administered by systemic route like ziconotide.

The first intrathecal use of bolus morphine for cancer pain analgesia was described by Wang in 1979 (3). Neuraxial infusion systems with internal pumps have now been available for more than 40 years (4). Following these seminal papers, other studies have confirmed that this is a valuable option for the small proportion of highly distressed cancer patients with pain refractory to all other analgesic treatments. For these patients, outcomes relating to pain and quality of life have been observed to have improved. (5, 6). Cancer pain treatment guidelines now include this therapy as an alternative for

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refractory pain (7, 8). Various retrospective, prospective, observational, and randomized controlled studies have shown its efficacy specifically in treating cancer related pain syndromes. (9-11) . IDDS have multiplied in recent years not only in the treatment of pain and spasticity, but also in the implementation of certain treatments that do not cross the blood brain barrier such as chemotherapy.

Most often, the treatment is delivered by a programmable pump, which is surgically implanted in the subcutaneous tissue from the anterolateral abdomen and anchored to the underlying fascia using nonabsorbable sutures. The pump is connected to a multilayered catheter tunneled subcutaneously around the patient's flank to the posterior midline where it is anchored to the fascia before it penetrates the spinal canal and the intrathecal space. For cancer pain patients who have a short life expectancy and require chemotherapy, the catheter can be connected to a subcutaneous port and an external pump. Three implantable and programmable pumps are available worldwide: The first is the SynchroMed II (Medtronic®, USA), a titanium device measuring 8.75 cm in diameter with a 20- or 40 ml pump reservoir and a recessed central septum. The second is the Prometra II (Flowonix®, USA), -another titanium device with a diameter of 6.9 cm and a central raised septum. The third pump is the Siromed (Tricumed®, Germany), which has a 9 cm diameter and a central raised septum (Table 1). This paper will review imaging studies relevant to IDDS before implantation as well as during implantation, follow up, and device malfunction.

Table 1: internal intrathecal pumps available

Model	Diameter	Reservoir	Flow rate	MRI
Synchromed II	8,75 cm	20 or 40 ml	0,048 - 24 ml/D	3 T
Prometra II	6,9 cm	20 ml	0-28.8 mL/day	1,5 T*
Siromedes	9 cm	20 or 40 ml	0,25 - 3 ml/ d	3T

*Device must be previously emptied

1 - Intrathecal drug diffusion and Imaging

The understanding of delivery mechanisms has been greatly improved using MRI and drug diffusion can now be modeled according to patient, infusion level and flow rate.

Several elements, such as the physio-chemical properties of the molecules, lead to variations in the efficacy of the treatments administered. The highly lipophilic drugs pass quickly through the Pia mater and the white matter but will be as quickly absorbed at the dorsal horn, resulting in a high systemic absorption. On the other hand, the highly hydrophilic drugs tend to linger longer in the CSF (which is primarily composed of water) and reach the spinal cord receptors later, however a smaller proportion will be reabsorbed in the general circulation (12). CSF has a bidirectional pulsatile flow due to the arterial pulse and to respiration-induced trans-thoracic pressure variations (13). These movements are not linear. Thanks to MRI imaging, we know that CSF flow variations depend on the spinal level and the positioning of the patient (14). Physical parameters also lead to individual variations. The subdural space presents a particular anatomy, non-linear and with inter-individual variation

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(15). These flow variations lead to a different dissemination in a given patient depending upon the positioning of the catheter tip.

Variations in diffusion speed and surface area are described as a function of the injection site, with greater diffusion cranially than caudally (16). Correlations between the heart and respiratory rate and variations in the speed of respiratory movements have also been described. increasing heart rate also increases displacement (17). Thanks to cine MRI measurement of CSF flow velocities, Hsu highlighted that as the heart rate increases, the CSF flow increases, and the diffusion of the molecule increases. (13). Moreover, continuous administration provides a different diffusion profile compared to that of bolus administration. Tangen (16) describes this wider diffusion profile during bolus administration, which could provide a new treatment option for some patients.

All of these mechanisms are intertwined. A reliable assessment of the exact diffusion via molecule migration analysis could help optimize intrathecal treatments and define the most appropriate mode (bolus or continuous). Different models are currently under study and should take off in the coming years. Recently a PET CT scan analysis via the administration of a labelled isotope has been described in animal models. (18, 19) Evaluating the CSF volume and movements is also a recent option via dynamic MRI. This could allow for the determination of the individual dose needed to reach the target, and whether a constant administration is more or less effective than a bolus mode. Tangen et al (16) proposes a promising in vitro model of intrathecal drug diffusion inside the CSF.

Finally, with the help of computerized modelling, new technologies like MRI and PET CT scan will soon be helpful in non-responder patients to better evaluate drug diffusion. Optimal efficiency could be obtained through the coordination of administration mode, molecule choice, and daily dosage determination.

2- Pre-implantation imaging

Intrathecal pumps are commonly placed in patients with refractory pain, of which intractable cancer pain is the leading indication (11, 20, 21). Understanding disease extension may allow pain physicians to anticipate clinical prognosis and complications such as epidural spinal cord compression or the development of new pain generators. In 2013, Chai et al reported two cases of patients treated with IDDS who developed epidural spinal cord compression from cancer progression after recent intrathecal therapy initiation (22). Pre-implantation imaging may allow the detection of asymptomatic or minimally symptomatic, potentially severe conditions such as epidural metastatic disease, which can block catheter implantation inside the CSF. It may also help to determine the proper entry site and optimal catheter tip placement.

Moreover, in cancer patients, the main contraindication is brain metastasis with intracranial hypertension. For this imaging, plain radiology is ineffective. CT Scan, including brain, thorax and abdominal imaging seems more efficient to better visualize the pre-operative status. Nevertheless, in some cases, MRI is mandatory to obtain accurate details regarding spinal cord compression and spinal canal anatomy before implantation (Figure 1). PET scans can better evaluate the potential evolution of cancer and pain in order to choose the best intrathecal approach.

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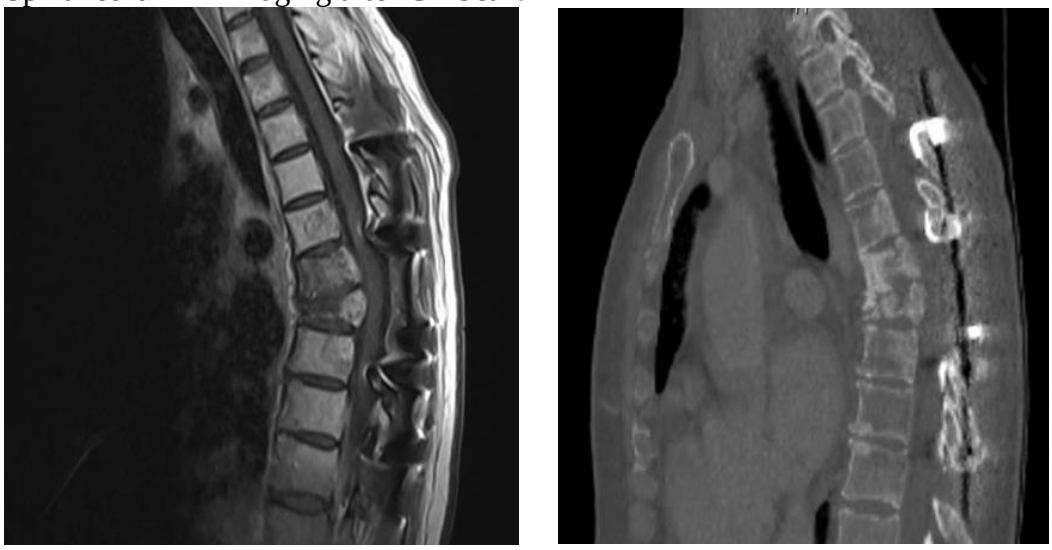
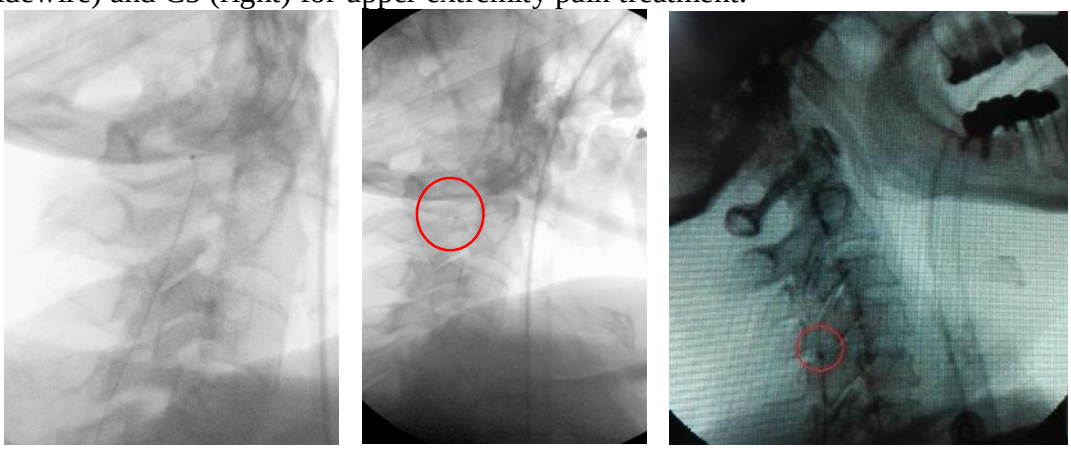
Figure 1: symptomatic epidural spinal cord compression diagnosed before system implantation, Spinal cord MRI imaging after CT Scan.



3 - Imaging during surgical implantation for optimal catheter placement

This neuromodulation technique delivers low doses of analgesics through a subarachnoid catheter. Limited intrathecal diffusion has been proven in animal models, computer simulations and in humans using different flow-rate models similar to those delivered by programmable IDDS (16, 23, 24). Current guidelines recommend placing the catheter tip close to the target receptors of the spinal segment(s) associated with the dermatome of the primary pain generator (25). Correct posterior placement concordant with the pain generator is also essential for targeted therapy (23). Fluoroscopy may allow for the correct visualization of the catheter tip and the confirmation of cephalocaudal and antero-posterior position. For head and neck cancer pain and upper limb pain, the catheter must be in cervical position. A C1 – C2 position for trigeminal pain (26) and a C4-C5 position for upper limb pain at the level of cervical plexus root are most appropriate (Figure 2).

Figure 2. Intrathecal catheter tip placed behind the spinal cord to C1 (left: with and without the guidewire) and C5 (right) for upper extremity pain treatment.



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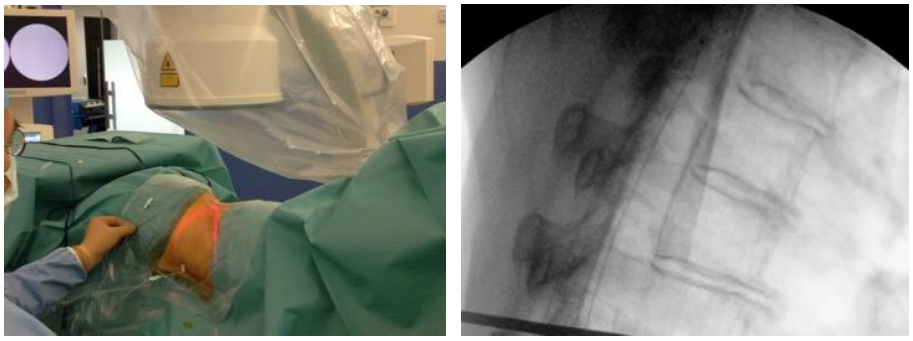
Real time imaging is required for optimal system implantation, as catheter placement is fundamental for targeted drug delivery (21, 25). Optimal placement requires access to the intrathecal space and a catheter positioning appropriate for the pain generator. Intrathecal drug delivery systems pumps are radiopaque, but newer catheters such as the Ascenda® (Medtronic, USA) are less radiopaque, excepting the catheter tip (Figure 2)

Fluoroscopy: For Intrathecal access, fluoroscopy in frontal projection is useful via a paramedian oblique approach. The needle is inserted into the intrathecal space at an angle of approximately 30°, until the dura is penetrated (27). Sagittal projection is the most common image guiding method used during surgery, as it is mandatory to implant the tip of the catheter behind the spinal cord (12) (figure 3). Myelography through the catheter can also be helpful to ensure correct intrathecal position.

Figure 3: Positioning of intrathecal catheter under sagittal fluoroscopy



Cone beam CT: Cone beam CT (CBCT) is an imaging modality that may facilitate IT catheterization in patients with complex anatomy. CBCT uses 3-D rotational fluoroscopy allowing fast visual feedback and surgical guidance. A study by Robinson evaluated the use of CBCT for IT access in fifteen consecutive patients with instrumented fusion for neuromuscular scoliosis, with all of the fusions extending from the upper thoracic spine to the sacrum. The procedure was technically successful in all cases (28). This modality nonetheless may require trans-operatory patient transport when hybrid suites are not available.

Intraoperative CT scan could also be an option to aid accurate intrathecal catheter positioning but so far, only an experience of deep brain stimulation lead implantation has been published (29).

4 - Device monitoring

The third major function is the role of imaging in the determination of a malfunctioning device. Visualization of the pump, the catheter, and its connections is performed after device implantation and during evaluation for potential system malfunction. This is to evaluate the pump and catheter positioning and medication flow, as the system lacks overpressure and flow alarms. Most of the drug delivery device-related adverse events are caused by intrathecal catheter failure, which are radio lucid excepting the tip (30)

Plain Radiography: Plain radiography performed in several projections is traditionally the first-line diagnostic tool (31-33). This may allow for the detection of pump turnover as the pump is asymmetric but is rarely helpful in detecting catheter-related complications due to the poor visibility of the

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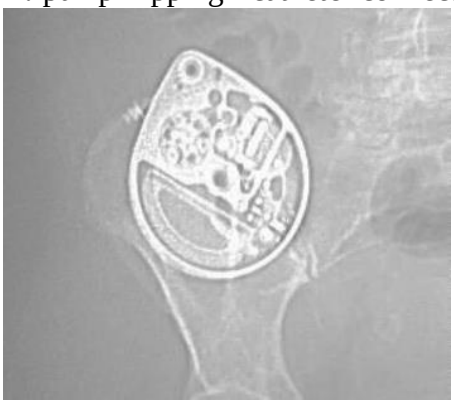
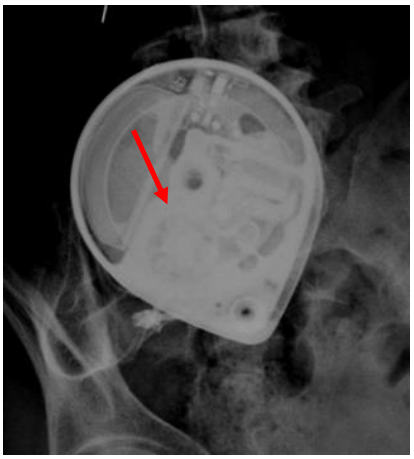
new Ascenda catheter, contrary to other radiopaque catheters.[26]. Plain radiology has a more limited role with new catheters (Ascenda Medtronic®) with poor opacity but remains useful for motor stall controlling rotation of the peristaltic pump and is appropriate for pump rotation diagnosis The catheter connection is counter-clockwise after the pump rotates (Figure 4).

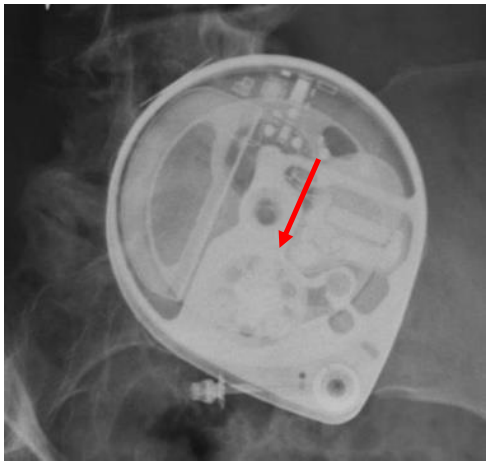
Figure 4: pump flipping - catheter connection is counterclockwise



X-ray fluoroscopic imaging, also allows for the dynamic rotor assessment of the Synchromed II pump (Figure 5) and the detection of an obstruction or a gross catheter leak. A dynamic fluoroscopy is performed by first aspirating 2 mL of fluid from the accessory port to avoid rapidly delivering the residual catheter medication to the patient during subsequent contrast injection (33).

Figure 5: rotors movements





Computer Tomography: Conventional CT scan after contrast injection may allow for the evaluation of a malfunctioning intrathecal pump (33) . New software-based 3-D CT reconstructions has been studied for optimal system morphological evaluation (34-36). 3-D computed tomography reconstruction is essential to follow the course of the catheter and to delineate distal catheter tip location. CT studies allow the monitoring of complications such as pump turnover after anchoring suture loss. 3-D

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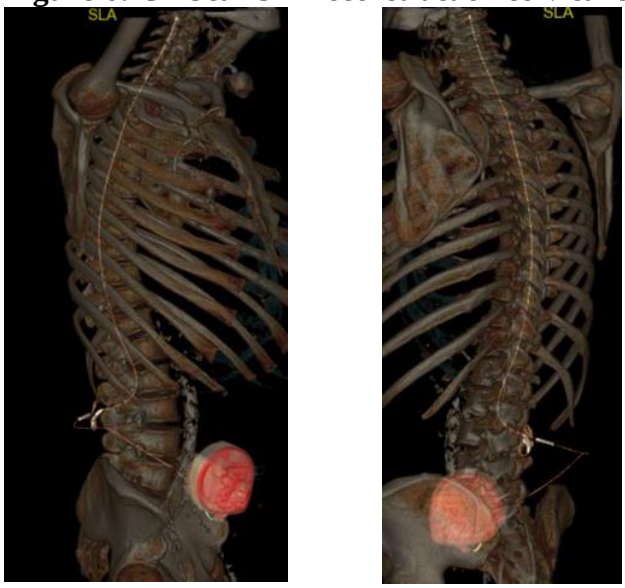
reconstructions may optimize visualization and surgical revision planning, as pain physicians may need to decide whether a dorsal or an anterior incision is necessary based on 3-D CT reconstruction (34)

Intrathecal catheter migration and infusion disturbances are potential risks even after long term therapy, recent trauma, or loss of therapy efficacy. In these situations, proper imaging is required for diagnosis. In a phantom study, low dose 3-D CT was used for device monitoring and Sn100 kVp offered the most advantageous trade-off between visibility, artifacts, and noise for a fixed dose. Researchers could correctly identify the catheter and related structures, using acceptable radiation exposure (37). 3-D CT reconstructions are routinely requested for cervical and cisternal placed catheters. (Figure 6).

CT scan imaging with the help of High resolution three-dimensional reconstruction allows more accurate control of catheter positioning and can easily diagnose dislodgment, kinking, and breaking (34, 36). High-resolution 3-D CT can identify IDDS complications with more precision than axial CT and fluoroscopy. Although contrast fluoroscopy provides an immediate, real-time way to evaluate the existence of many flow-obstructing or flow-redirecting defects within the intrathecal pump-catheter hardware, high-resolution CT may be better for evaluating slow leaks due to high-resistance defects such as microfractures (35).

When a catheter leak is suspected, and routine contrast fluoroscopy is unrevealing, post-injection 3D-CT reconstruction should be performed to further investigate the possibility of a subtle leak. In a study by Morgalla et al, for 22 complications. 3-D-CT had a 58.93% -100% (CI 95%) sensitivity and 87.54% - 100% (CI 95%) specificity (36). In a recent study Delhaas et al analyzed data of 70 catheter access port Computed Tomography Myelography procedures with 2-D/3-D reconstructions of 53 adult patients where the cause of treatment was unclear. The authors found post-injection 3-D-CT reconstruction to have a sensitivity of 81% and a specificity of 93% (38).

Figure 6: CT Scan 3-D reconstruction cervical catheter



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Radio isotope imaging procedure: As infusion flow rate is low, diffusion control requires dynamic imagery which can be performed by TC99 scintigraphy, facilitating the visualization of drug diffusion inside the device and the CSF, as well as the drug velocity (39). A recent proof of concept study in piglets has validated the injection of a radioligand into subarachnoid space during positron emission tomography (PET) scanning. In the near future, PET- CT scan could be useful for testing the distribution of PET-tracers for pharmaceuticals targeting the central nervous system and the spinal cord(18).

Other more laborious methods, such as a low-dose radioisotope imaging procedure, may be considered (39). Nuclear Scintigraphy Radionuclide flow studies consist of the injection of radioisotopes into the pump reservoir to evaluate the pump system functionally. In a study using Indium-111, DTPA was injected at a dose of 0.5–0.6 mCi into the reservoir without interrupting the delivery of medications. Researchers reviewed 23 studies in 19 patients following the injection, demonstrating eight (35%) malfunctioning systems; 6 of whom were subsequently treated surgically.

Another study described findings in 11 patients investigated for catheter malfunction using Technetium-99m DTPA. Loss of catheter potency was demonstrated in six patients, enabling the identification of the blockage site. The authors administered 40MBq of Technetium-99m DTPA in 1 ml to all patients. This required prior reservoir emptying. The isotope was then delivered in two consecutive 0.5ml boluses. Images from 1 hour after administration and 3–4 hours after administration were used to assess whether the system successfully delivered the isotope to the cerebrospinal fluid. All isotope images were acquired on a single-headed gamma camera with a general-purpose collimator. The effective dose per patient in this study was low (1.3 mSv) (40).

Magnetic Resonance Imaging. Performing an MRI scan at 1,5 Tesla (Prometra®) to 3 Tesla (Synchromed II®) is possible with an IDDS, however pumps need to be checked just after to avoid motor stall (41). MRI is the most accurate imagery to diagnose spinal cord injuries following implantation or as an adverse effect of IT treatment such as granuloma whose incidence is 1% (42). Patients with implanted drug delivery systems with the catheter tip located in the lumbar cistern may develop new onset lumbar radicular pain as a result of catheter migration into an intervertebral foramen (43). Magnetic resonance imaging (MRI) is recommended as the initial imaging study to survey the spine in new onset radicular pain, which may in cases of high concentration and low flows be related to intrathecal granuloma formation (42, 44, 45). MRI compatibility has been validated clinically in a single-center, 3-year, prospective evaluation in forty-three consecutive patients with an implanted programmable SynchroMed® II IDDS and requiring an MRI (1.5-tesla). None of the patients experienced technical or medical complications (41). Nonetheless, due to the observation of post-MRI pump malfunctions in several case reports, we currently perform pump interrogation on all patients with IDDS after MRI to ensure the proper functioning of the pump (46).

Ultrasound guided refill technique: Poor accuracy in identification of intrathecal pump septum can lead to life-threatening complications such as the accidental subcutaneous injection of high-dose opioids (46, 47). Because the pump is made of titanium, it reflects ultrasound echoes and appears as a highly echogenic outline, but the silicone septum is easily visualized as a hypoechoic rectangular structure (figure 7).

This allows for the visualization of the reservoir and may be useful to ensure higher success of refill, particularly in difficult cases relating to obesity and pumps

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placed deeper than 10mm (48) (Figure 7). Ultrasound may assist in finding the silicone septum during refills of non-raised septum devices performed by inexperienced providers or in deeply-placed devices (49). Ultrasound may allow the marking of the silicone septum and decrease the number of attempts to enter the reservoir fill port compared to the blind technique. This does not appear to be the case for raised septum devices (49). Regarding patient center outcome, another study found ultrasound guidance was the preferred method for patients compared to template-guided procedures even though it lengthened the duration of refills. Fewer patients experienced procedural pain with ultrasound compared with template-guided refills. No safety issues were observed in either group (50) . In addition, ultrasound permitted the identification of potential complication such as CSF fistula and subcutaneous collections (Figure 8). It may also assist clinicians to detect pumps that have flipped as surface echography will only reveal a solid hyper echoic outline.

Figure 7: Ultrasound image from a 12 MHz linear probe scan of anterior abdominal wall facing intrathecal pump, the silicon recessed septum is visible allowing device access.

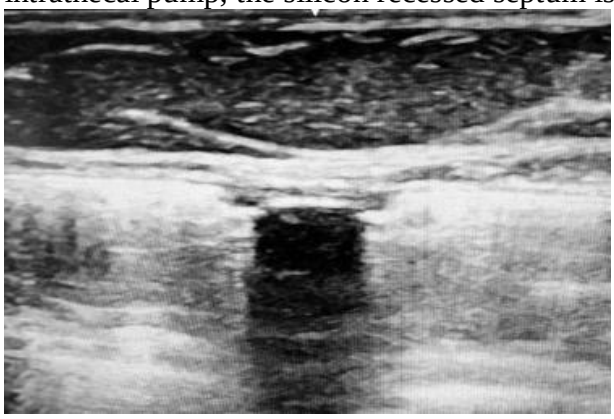
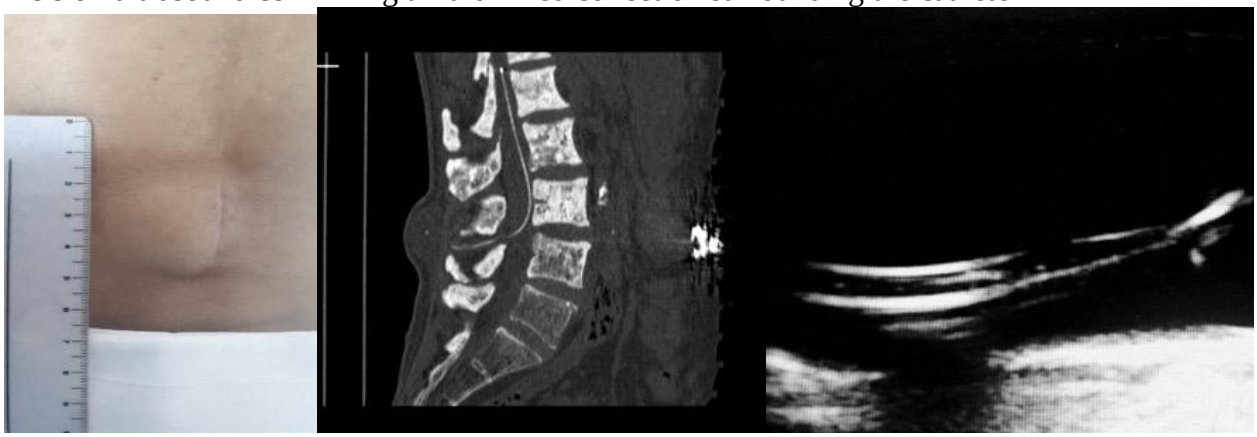


Figure 8: Cerebrospinal fluid fistula: A) Intrathecal catheter adequately placed in a patient with extensive metastatic spine disease and a fluid-filled collection in her dorsal incision. B) Dorsal incision ultrasound confirming a fluid-filled collection surrounding the catheter



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Other methods: In exceptional cases of vascular complications form repeated blunt trauma, the use of angiograms has been described for inferior epigastric artery erosion from a lower quadrant placed pump (51).

Conclusions:

Intrathecal Drug delivery Systems are invasive pain treatment therapies requiring implantation of a catheter inside the CSF connected to a subcutaneous pump bypassing Blood Brain Barrier. IDDS has developed considerably over the last few decades and is now widely recommended, especially in patients with refractory cancer pain. Imaging is a key element in understanding the drug diffusion and is essential before and during implantation. It also provides invaluable aid in the diagnosis of complications. We reviewed state-of-the-art evidence regarding IDDS imaging during preimplantation, during surgery, and after implantation for assessing device function and optimizing treatment patterns. Medical imaging has a key role in IDDS treatment. In the future, imaging could also be a great help to model intrathecal drug distribution.

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