# Ultravision joins the fight against peritoneal cancer

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## Considering the high, unmet medical need associated with peritoneal metastases, Dr Dominic Griffiths, CEO of Alesi Surgical Ltd, outlines how the company's innovative Ultravision technology could dramatically improve clinical outcomes for patients with the disease

Peritoneal metastases (PM) refers to cancer that has spread from primary cancer in other organs in the abdomen to the peritoneum, the membrane that lines the abdominal cavity. According to the WHO, there are over seven million new primary abdominal cancer cases each year [(1)], and depending upon the primary cancer, up to 60% of these will present evidence of PM. [(2)]

As a result, it is estimated that every 30 seconds, a patient is diagnosed with peritoneal metastases. In most cases, at diagnosis, it is typically an advanced, incurable disease. Current therapy guidelines recommend palliative systemic chemotherapy. However, with poor blood supply to the peritoneum, efficacy is poor, and side effects are debilitating. As a result, this terrible disease has a poor prognosis, with patient survival worse than lung and liver metastases. [(3)] It remains a high, unmet medical need.

### PIPAC hailed as an innovative treatment

Pressurised intra-peritoneal aerosolised chemotherapy (PIPAC) is a new, minimally invasive chemotherapy delivery method for peritoneal metastases patients. PIPAC is a laparoscopic procedure that delivers chemotherapy directly to the abdomen.

The benefits of laparoscopic surgery, of improved patient recovery times and enhanced outcomes, are widely acknowledged, and local delivery of chemotherapy has the potential to avoid the need for higher systemic doses. High local drug concentration and low toxicity have meant that PIPAC has been hailed as an innovative treatment with considerable potential. However, PIPAC has recognised limitations: [(4)]

Suboptimal distribution: PM is rarely localised; therefore, the ideal treatment would maximise drug distribution throughout the abdominal cavity. Although delivered as an aerosol, the predominant force acting upon the aerosol in PIPAC is gravity, meaning that drug deposition is typically concentrated directly beneath the pressurised injector and on the lower surfaces of the abdomen.

Suboptimal tumour penetration by the chemotherapy drugs: although delivering chemotherapy locally overcomes some of the issues associated with systemic drug delivery, the challenge of tumour penetration and drug uptake remains. Tumour tissue is

generally resistant to drug uptake when applied locally. This means that drug penetration favours the penetration of healthy rather than cancerous tissue.

Prolonged drug sedimentation times: it is generally accepted that smaller drug-containing particles are more effective in penetrating tumours. The consequence of “nanoparticle” delivery is that the time taken for drug sedimentation (i.e., by gravity) dramatically increases, prolonging procedure time. Paradoxically, larger particles sediment faster yet are less effective; smaller particles will not sediment quickly but are more effective.

Contamination of surgical instruments and surfaces: chemotherapy drugs are cytotoxic, and a major challenge to PIPAC adoption is the risk that such aerosolised chemotherapy drugs represent to healthcare professionals performing these procedures. As a result, PIPAC is currently only undertaken in selected centres, using specialised operating rooms and personnel.

Ultravision is a proprietary system developed by Alesi Surgical (Cardiff, UK) to handle the bioaerosols – commonly called surgical smoke – created by energy-based instruments during laparoscopic surgery. Ultravision improves surgical visibility and prevents the release of these potentially hazardous bioaerosols into the operating room. [5] The system uses electrostatic precipitation (EP), an “electrical filtration” technology widely used in other industries for removing fine particles from the atmosphere with very high efficiency.

It comprises a generator unit, an active electrode, and a patient return electrode. When introduced into the abdomen, electrons emitted from the active electrode create negatively charged gas ions, which migrate rapidly to the patient tissue because of the electrical potential difference between the electrode and the patient. As they migrate, these ions collide with any aerosolised particles, causing an electrostatic attraction of the negatively charged particles to the tissue surfaces of the peritoneum, dramatically accelerating their deposition.

## Developing an optimised UltraPIPAC system

The ability of Ultravision to accelerate the deposition of aerosolised matter, preventing its release into the operating room and potentially enhancing drug distribution has been recognised by healthcare professionals. This led to its “off-label” use in the PIPAC procedure. Five independent clinical publications now report Ultravision’s use in 440 PIPAC procedures on 172 patients.

Whilst these papers support the safety of this approach, Ultravision was not specifically developed for this purpose. The first in human study demonstrated that its use induces regression of PM in biologically aggressive tumours. [6]

In contrast, two clinical papers confirmed the need to optimise the current system and protocol, reporting insufficient tumour response [7] and excessive systemic absorption. [8] Whilst its potential was demonstrated, the need for optimisation of the system and protocol was equally clear.

Following the award of a European Innovation Council Accelerator (EIC) grant, Alesi can now reprofile the Ultravision technology to revolutionise PIPAC. The project involves the development of a new, optimised generator and multi-electrode system for the delivery of chemotherapeutic aerosols. “UltraPIPAC” has the potential to improve the safety and efficacy of chemotherapeutics used to treat PM by improving localised drug distribution and tissue uptake, minimising dose requirements, reducing overall procedure time, and avoiding dangerous aerosol contamination in the operating room.

Initial preclinical and clinical studies have shown that EP using Ultravision significantly improves aerosol distribution. [9] Aerosolised nanoparticles remain stable in vitro, while EP significantly improved the spatial homogeneity of their distribution. EP also significantly enhances tissue penetration, spatial homogeneity, and tissue uptake after intraperitoneal nebulisation of anticancer nanoparticles. [10]

The project involves working closely with the PIPAC community. Alesi has engaged a world-class Medical Advisory Board, comprising Professors Jared Torkington (Cardiff, UK), Wim Ceelen (Gent, Belgium), Ignace de Hingh (Eindhoven, Netherlands), and Drs Naoual Bakrin (Lyon, France) and Martin Graversen (Odense, Denmark). All are pioneers in this field, with over 65 papers published on the subject.

The project team is also working with Professor Ceelen’s laboratory in Gent, which has developed specialised techniques that will define the performance specification of the new system and undertake its characterisation throughout its development.

The successful development of UltraPIPAC will result in improved outcomes for patients suffering from this terrible disease. PIPAC’s use is currently restricted to use in patients that are unresponsive to palliative systemic chemotherapy. Successfully combining Ultravision with PIPAC will culminate in a ground-breaking innovation for patients and physicians, helping this localised and revolutionary approach move earlier in the treatment pathway.

**References**


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