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thesynapse

THE MEDICAL PROFESSIONALS' NETWORK

Fertility Preservation Strategies in Early-Stage Cervical Cancer

Neuraxial Anaesthesia in the Parturient with Multiple Sclerosis

Towards Sustainable Ophthalmology

Breast MRI - No Time Like the Present

UNITED FOR LONG-LASTING† LDL-C CONTROL[1]

LEQVIO is administered every 6 months* and provides effective LDL-C control, supported by 6+ years of data[1,2]

*Two doses a year after the two initial doses. Single subcutaneous injection at the start of treatment, again at 3 months, and thereafter every 6 months.[1]
†LDL-C reduction was maintained during each 6-month dosing interval after 2 initial doses of inclisiran.

LEQVIO®
inclisiran

▼ LEQVIO®

PRESENTATION: Leqvio 284 mg solution for injection in prefilled syringe. Each pre-filled syringe contains inclisiran sodium equivalent to 284 mg inclisiran in 1.5 ml solution. Each ml contains inclisiran sodium equivalent to 189 mg inclisiran.

INDICATION: Leqvio is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet: in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

DOSAGE: The recommended dose is 284 mg inclisiran administered as a single subcutaneous injection: initially, again at 3 months, followed by every 6 months. • *Missed doses:* If a planned dose is missed by less than 3 months, inclisiran should be administered and dosing continued according to the patient's original schedule. If a planned dose is missed by more than 3 months, a new dosing schedule should be started – inclisiran should be administered initially, again at 3 months, followed by every 6 months. • *Treatment transition from monoclonal antibody PCSK9 inhibitors:* Inclisiran can be administered immediately after the last dose of a monoclonal antibody PCSK9 inhibitor. To maintain LDL-C lowering it is recommended that inclisiran is administered within 2 weeks after the last dose of a monoclonal antibody PCSK9 inhibitor. • *Elderly, hepatic impairment, renal impairment:* no dose adjustment is necessary. Inclisiran should be used with caution in patients with hepatic and renal impairment.• *Paediatric population:* The safety and efficacy of inclisiran in children aged less than 18 years have not yet been established. • *Method of administration:* Inclisiran is intended for administration by a healthcare professional via subcutaneous route. Each pre-filled syringe is for single use only.

CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients listed in the SmPC.

WARNINGS/ PRECAUTIONS: • *Haemodialysis:* The effect of haemodialysis on inclisiran pharmacokinetics has not been studied. Considering that inclisiran is eliminated renally, haemodialysis should not be performed for at least 72 hours after inclisiran dosing. • *Sodium content:* This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

INTERACTIONS: Inclisiran is not an inhibitor or inducer of cytochrome P450 enzymes or common drug transporters. Therefore, inclisiran is not expected to have clinically significant interactions with other medicinal products. Based on the limited data available, clinically meaningful interactions with atorvastatin, rosuvastatin or other statins are not expected.

PREGNANCY, LACTATION AND FERTILITY: • There are no or limited amount of data from the use of inclisiran in pregnant women. As a precautionary measure, it is preferable to avoid the use of inclisiran during pregnancy. • It is unknown whether inclisiran is excreted in human milk. A risk to newborns/ infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from inclisiran therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. • No data on the effect of inclisiran on human fertility are available.

ADVERSE REACTIONS: *Common:* Adverse reactions at the injection site.

LEGAL CATEGORY: POM

PACK SIZES: Pre-filled syringe: x1 pre-filled syringe. Pre-filled syringe with needle guard: x1 prefilled syringe with needle guard.

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland.

MARKETING AUTHORISATION NUMBER: EU/1/20/1494/001-2

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa MRS 1000 Malta. Tel +356 21222872.

2022-MT-LEQ-24-MAR-2022

References: 1. Leqvio Summary of product characteristics. Novartis. August 2022. **2.** RS Wright, FJ Raal, W Koenig, U Landmesser, LA Leiter, GG Schwartz, A Lesogor, P Maheux, Z Talloczy, S Vikarunnessa, X Zang, KK Ray. ORION-8: Long-term efficacy and safety of twice-yearly inclisiran in high cardiovascular risk patients. Data presented at the ESC Congress on August 28, 2023.

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The day you choose **JAKAVI®** (ruxolitinib) **is the day you could change their life**[1-5]

RESPONSE | CONTROL | SURVIVAL

JAKAVI is indicated for the treatment of adult patients with myelofibrosis (MF), including primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.[1]

JAKAVI® ruxolitinib

PRESENTATION: Each tablet contains 5mg, 10mg, 15mg or 20mg Ruxolitinib **INDICATIONS:** Jakavi is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis. Jakavi is indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant to hydroxyurea. Jakavi is indicated for the treatment of graft host versus host disease or chronic graft versus host disease in patients over the age of 12 who have inadequate response to corticosteroids or other systemic therapies. **DOSAGE:** Jakavi treatment should only be initiated by a physician experienced in the administration of anti cancer medicinal products. A complete blood cell count, including a white blood cell count differential, must be performed before initiating therapy with Jakavi. The recommended starting dose in MF is of 5mg ruxolitinib twice daily for patients with platelet count between 50,000/mm^3 and 75,000/mm^3, 10mg twice daily for patients with platelet count from 75,000/mm^2 to 100,000/mm^2, 15 mg ruxolitinib twice daily for patients with a platelet count between 100,000/mm^3 and 200,000/mm^3 and 20 mg twice daily for patients with a platelet count of >200,000/mm^3. Treatment may be continued as long as the benefit-risk remains positive. However the treatment should be discontinued after 6 months if there has been no reduction in spleen size or improvement in symptoms since initiation of therapy. Jakavi is to be taken orally, with or without food. If a dose is missed, the patient should not take an additional dose, but should take the next usual prescribed dose. The recommended dose for PV is 10mg given orally twice daily. Treatment should also be interrupted when haemoglobin is below 8g/dl. After recovery of blood counts above these levels, dosing may be restarted at 5mg twice daily and gradually increased based on careful monitoring of complete blood count. Dose reduction should also be considered if haemoglobin decreases below 12g/dl and is recommended if it decreases below 10g/dl. If efficacy is considered insufficient and blood counts are adequate, doses may be increased by a maximum of 5mg twice daily, up to a maximum dose of 25 mg twice daily. The recommended dose in GvHD is 10mg given orally twice daily. It can be added to continued corticosteroid use and/or calcineurin inhibitors (CNIs). Dose reductions and temporary interruptions of treatment may be needed in GvHD-patients with thrombocytopenia, neutropenia, or elevated total bilirubin after standard supportive therapy including growth-factors, anti-infective therapies and transfusions. In GvHD, tapering of Jakavi may be considered in patients with a response and after having discontinued corticosteroids. A 50% dose reduction of Jakavi every two months is recommended. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. Pregnancy and lactation. **WARNINGS/PRECAUTIONS:** Treatment with Jakavi can cause haematological adverse drug reactions, including thrombocytopenia, anaemia and neutropenia. A complete blood count, including a white blood cell count differential, must be performed before initiating therapy with Jakavi. Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal and viral infections. Tuberculosis has been reported in patients receiving Jakavi. Before starting treatment, patients should be evaluated for active and inactive ("latent") tuberculosis, as per local recommendations. Hepatitis B viral load increases have been reported in patients with chronic HBV infections taking Jakavi. Therefore such patients should be treated and monitored according to clinical guidelines. It is recommended to screen for HBV prior to commencing treatment with Jakavi. Physicians should educate patients about early signs and symptoms of herpes zoster, advising that treatment should be sought as early as possible. Progressive multifocal leukoencephalopathy (PML) has been reported with Jakavi treatment for myelofibrosis. Non-melanoma skin cancers have been reported in patinets treated with ruxolitinib. Periodic skin examination is recommended for patients who are at risk for skin cancer. Treatment with Jakavi has been associated with increased lipid parameters and therefrore lipid monitoring and treatment of dyslipidemia according to clinical guidelines is recommended. The starting dose of Jakavi should be reduced in patients with severe renal impairment. For patients with end-stage renal disease on haemodialysis the starting dose should be based on platelet counts. The starting dose of Jakavi should be reduced by approximately 50% in patients with hepatic impairment. Following interruption or discontinuation of Jakavi, symptoms of myelofibrosis may return over a period of approximately one week. There have been cases of patients discontinuing Jakavi who sustained more severe events, particularly in the presence of acute intercurrent illness. Jakavi contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. **INTERACTIONS:** Interaction studies have only been performed in adults. When administering Jakavi with strong CYP3A4 inhibitors the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily. Patients should be closely monitored (e.g. twice weekly) for cytopenias and dose titrated based on safety and efficacy. Patients should be closely monitored and the dose titrated based on safety and efficacy. In healthy subjects given ruxolitinib (50 mg single dose) following the potent CYP3A4 inducer rifampicin (600 mg daily dose for 10 days), ruxolitinib AUC was 70% lower than after administration of Jakavi alone. No dose adjustment is recommended when ruxolitinib is co-administered with mild or moderate CYP3A4 inhibitors (e.g. erythromycin). There is no interaction study with oral contraceptives. It cannot be excluded that ruxolitinib inhibits CYP3A4 in the intestine. Ruxolitinib may inhibit P-glycoprotein and breast cancer resistance protein (BCRP) in the intestine. This may result in increased sytemic exposure of substrates of these transporters, such as dabigatran etexilate, ciclosporin, rosuvastatin and potentially digoxin. The concurrent use of haematopoietic growth factors and Jakavi has not been studied. The concomitant use of cytoreductive therapies and Jakavi has not been studied. The safety and efficacy of this co-administration is not known. **ADVERSE REACTIONS:** MF patients – Very common: Urinary tract infections, Herpes zoster, Pneumonia, Anaemia, Thrombocytopenia (any CTCAE grade and CTCAE grade 3), Neutropenia (any CTCAE grade), Bleeding (any bleeding including intracranial bleeding, gastrointestinal bleeding other bleeding), Bruising, Gastrointestinal bleeding, Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria), Hypercholesterolaemia (any CTCAE grade), Hypertriglyceridaemia (any CTACAE grade), Weight gain, Dizziness, Headache, Elevated lipase (any CTCAE grade), Constipation, Raised alanine aminotransferase (any CTCAE grade), Raised aspartate aminotransferase (any CTCAE grade), Hypertension. Common: Sepsis, Thrombocytopenia (CTCAE grade 4), Neutropenia (CTCAE grades 3&4), pancytopenia, Intracranial bleeding, Flatulence, Raised alanine aminotransferase (CTCAE grade 3). PV patients – Very common: Urinary tract infections, Herpes zoster, Anaemia (any CTCAE grade), Thrombocytopenia (any CTCAE grade), , Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding), Bruising, Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria), Hypercholesterolaemia (any CTACAE grade), Hypertriglyceridaemia (any CTCAE grade), Weight gain, Dizziness, Headache, Elevated lipase (any CTCAE grade), Constipation, Raised alanine aminotransferase (any CTCAE grade), Raised aspartate aminotransferase (any CTCAE grade), Hypertension; Common; Pneumonia, Anaemia (CTCAE grade 3), Thrombocytopenia (CTCAE grade 3), Neutropenia (any CTCAE grade), pancytoenia, Gastrointestinal bleeding, Flatulence. For a full list of adverse reaction please refer to the Summary of Product Characteristics. **LEGAL CATEGORY:** POM **PACK SIZE:** 56 Tablets **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. **MARKETING AUTHORISATION NUMBER:** EU/1/12/773/005, 008, 011, 015.

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 21222872.2022-MT-JAK-29-APRIL-2022. To report adverse events electronically please use the following link: www.novartis.com/report or by e-mail at drug_safety.malta@novartis.com.

References: 1. JAKAVI® (ruxolitinib) Summary of Product Characteristics, April 2022. **2.** Verstovsek S, et al. N Engl J Med. 2012;366:799 807., **3.** Harrison C, et al. N Engl J Med. 2012;366:787–798. **4.** Verstovsek S et al. J Hematol Oncol. 2017; 10(1): 55. **5.** Verstovsek S et al. J Hematol Oncol. 2017; 10(1): 156.

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Issue Guide

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Personal Ponderations

It was a dry and sunny September morning when, in 2005, I paid a visit to Dr Wilfred Galea at his Dingli office. I remember that we discussed many topics that inevitably gravitated around my involvement with The Synapse medical magazine. This was followed, a few days later, by a second meeting at a corner bar in St Luke's square to discuss the metamorphosis of the monotone 8-pager, with the primary goal being the dissemination of relevant medical information to the busy healthcare professional.

I thus became the Managing Editor of the magazine. There is no need to explain the evolution of the publication. All of you are witness to its cathartic evolution. Along the years, a diverse set of contributors started being involved including distinguished lawyers, historians, pharmacists, doctors, as well as allied healthcare professionals. We introduced regular interviews with local and foreign trailblazers including the late Prof. Edward Debono, Prof. Dame Claire Gerada - former President of the RCGP, and Boston University's Robert A. Knox Professor Sandro Galea. Other distinguished characters such as Prof. Denis Horgan, who was a policy advisor in the European Parliament, contributed material to the magazine. Also, collaborations with student associations and medical associations were launched. My aim was always to communicate and build bridges. I strongly believe that if we speak and work together, we can naturally achieve our goals together.

If the readers don't mind a personal ponderation, the transmutation of the publication during the past two decades marked specific seminal changes in my life. Of note is the fact that I lost my father to pancreatic adenocarcinoma on the 3rd of July 2021, 2am. My father's disease gradually gutted me for 13 long months. It was living hell, which was made worse by radiotherapy machine breakages and industrial actions. During this period, I also started to discern true friendships, beyond my naïve predisposition.

Returning to the subject, each publication which, until recently was published six times a year, involved exhaustive discussions, planning, and editing. I still remember the bi-monthly nocturnal pre-publication meetings at Dr Galea's office which used to last till 1am, discussing the design and proof reading, over sandwiches and tea.

These two decades, during which I crossed paths with hundreds of healthcare professionals, have indeed been an enriching experience. I mastered the art of discipline and good governance, was taught to speak the truth, admit a mistake when this was made, and responsibly take disciplinary actions if need be, even if I did not like to do so. However, I have never been a demonizer or ruffian. I always strived to build bridges built on trust, believing that if we work together we can achieve our goals together. This was the raison d'etre at The Synapse which I fiercely assimilated by osmosis.

Why am I writing all this? Because these past few months were particularly challenging for me. In hindsight, this baptism of fire has strengthened me. Period.

I take the opportunity to convey the following three messages to the young ones. Just three.

1. Passionately build your legacy, with time, empathy and resilience as your confidants. Draw energy from positive people. Heed advice from the older generations whom you trust.
2. Have the guts to board a new train and equally, find in your inner self even more courage to step down. Believe in yourself. You are your greater strength.
3. Lead by speaking truth to power, knowing your limitations. This will earn you respect even though this is rarely shown to you.

The going is tough, very tough, but the future is bright. *'Justify the Ways of God to Men'* … reverberating words penned by John Milton in 1674, and still relevant to me in 2024.

DR JESSICA MUSCAT

Breast MRI - No Time like the Present

KEY WORDS
Breast imaging, Magnetic resonance imaging, Indications for breast MRI, High-risk screening, Breast density

INTRODUCTION

Breast imaging – as a radiological subspecialty – is perhaps the epitome of how the practice of radiology has changed through the decades. Imaging of the breast is an exciting and challenging combination of multimodality image acquisition, interpretation, biopsy procedures, clinical, radiological and radiopathological correlation. The breast radiologist is an integral part of the multidisciplinary team guiding patients on this most personal journey from diagnosis to an end-goal of survivorship and quality-adjusted life-years gained.

Breast magnetic resonance imaging (MRI) was introduced to the breast imaging community in the 1990s and has since then become a validated tool for the diagnostic evaluation of the breast. Compared to conventional imaging modalities, namely mammography and ultrasound, MRI has been proven to have a very high cancer detection sensitivity ranging between 93-100% albeit with a low specificity ranging between 37-97%.

In simplest terms, the physiological explanation for the high sensitivity of MRI for cancer detection is that contrast-enhanced MRI is extremely sensitive for tumour angiogenesis. The vessels formed by tumour angiogenesis are abnormal and more 'leaky' than native vessels. The increased enhancement of cancers relative to normal breast tissue may result from both an increased supply of contrast agent (gadolinium) through this proliferation of blood vessels and their increased permeability. Hence, breast MRI utilizes the dynamic (with time) contrast-enhancement (DCE) characteristics of lesions. Several sets of imaging are acquired at different time points. The increased leakiness of the abnormal vasculature results in earlier wash-out of contrast from malignant lesions when compared to normal breast parenchyma. The varying cyclical vascularity of the premenopausal breast actually determines the opportune timing (day 10 – 16 of menstrual cycle) of imaging examination.[1,2] Features such as restricted diffusivity and corresponding apparent diffusion coefficients of lesions can further differentiate benign from more suspicious findings.[3]

INDICATIONS

At present, there are no large-scale randomized controlled trials to support the widespread use of contrast-enhanced breast MRI in the general normal-risk population. MRI of the breasts has however been found to be merited in many specific situations. The purpose of this overview is to provide readers with a current outline of the indications for diagnostic breast MRI.[1,2,4]

ASSESSMENT OF DISEASE EXTENT: STAGING OF BREAST CANCER

MRI is the most sensitive method for breast cancer staging in the same or contralateral breast. Though not routinely included as part of the local staging workup in all diagnosed breast cancers, MRI is commonly used in these particular subgroups:

1. **Cancer of Unknown Primary** i.e. biopsy-proven axillary lymph node breast cancer secondary deposits with normal conventional imaging (mammography and ultrasound).
2. Assessing **pectoral muscle invasion** when clinical examination and conventional imaging is equivocal.
3. **Invasive lobular cancer** (ILC) is known to be under-diagnosed mammographically as its particular growth patterns are challenging to distinguish from normal breast tissue. ILC makes up to 15% of breast cancers and is more likely to present as an asymmetry or an architectural distortion on mammography with a reported mammographic sensitivity ranging from 34 to 92%. Even when detected on mammography, the modality tends to underestimate size. ILC is more frequently locally advanced at diagnosis and is generally a larger tumour at time of presentation than is invasive ductal carcinoma because it is more difficult to detect both clinically and on imaging.[1] MRI is the most sensitive technique for breast cancer staging in the same or contralateral breast in the context of a lobular breast cancer diagnosis[5] (Figure 1).
4. In patients with **ductal carcinoma in situ** (DCIS) MRI may help delineate extent and also potentially identify any invasive component (Figure 2).
5. In patients with **atypical ductal hyperplasia, lobular carcinoma in situ and atypical lobular hyperplasia** the high negative predictive value of DCE-MRI can exclude malignancy.[6]

Figure 1.

A. 53-year-old female presented with a palpable right lateral breast lump. This corresponds to a distorting lesion in the lateral right breast on CC view with no definite correlate on mediolateral oblique view.

B. Solid, vertically oriented, irregular lesion identified sonographically at site of palpable lump – sampling confirms a Grade 2 ILC.

C. MRI breast delineates known BIRADS 6 spiculate mass corresponding to Grade 2 ILC.

D. A second smaller suspicious enhancing mass lesion in a more anterior and caudal plane (biopsy at second-look US confirmed G1 ILC).

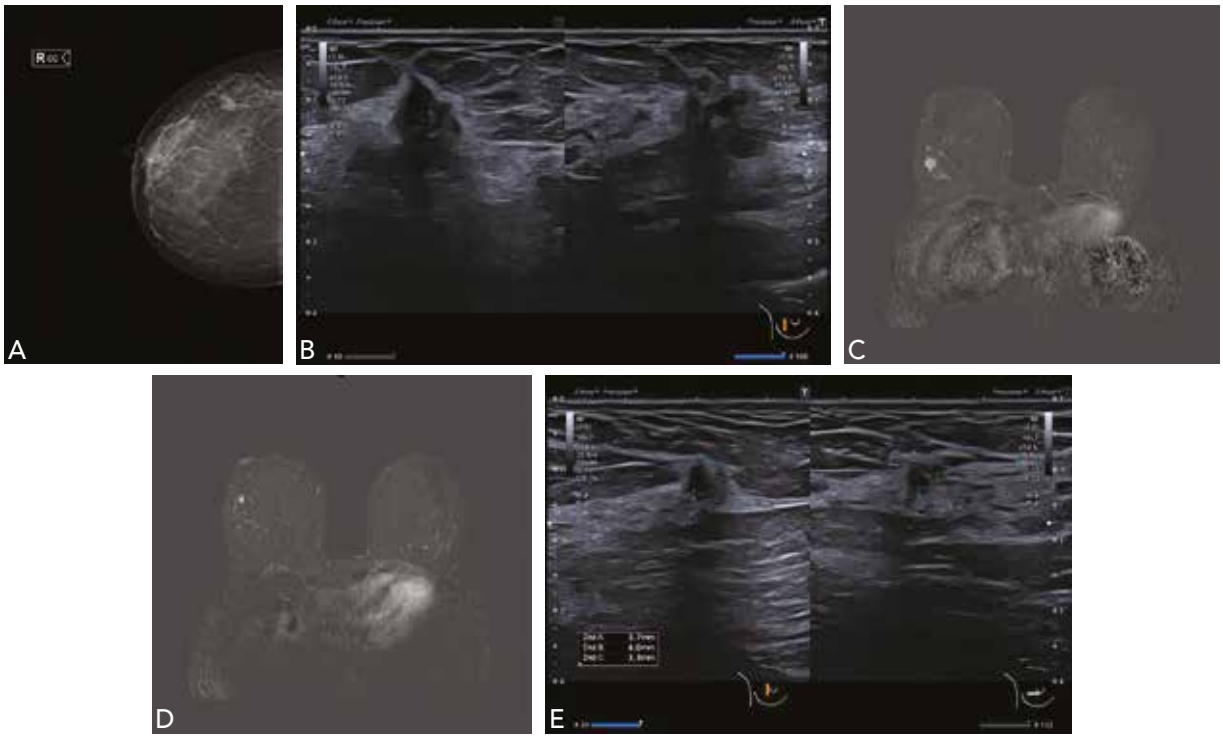


Figure 2.

A. 36-year-old presenting with a vague fullness in the medial breast. Mammography delineates medial fine clustered variable microcalcifications. Stereotactic sampling confirmed multiple foci of high-grade DCIS (B5a).

B. Segmental clumped enhancement across the left medial breast. Findings after left mastectomy confirmed a histological diagnosis of extensive high-grade DCIS, measuring 50mm, with a focus of invasive ductal carcinoma, 7mm maximum dimension.

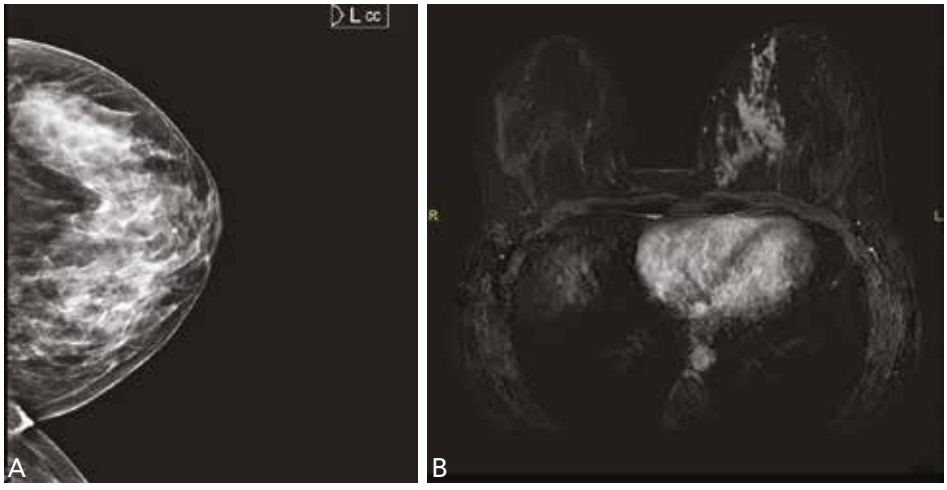
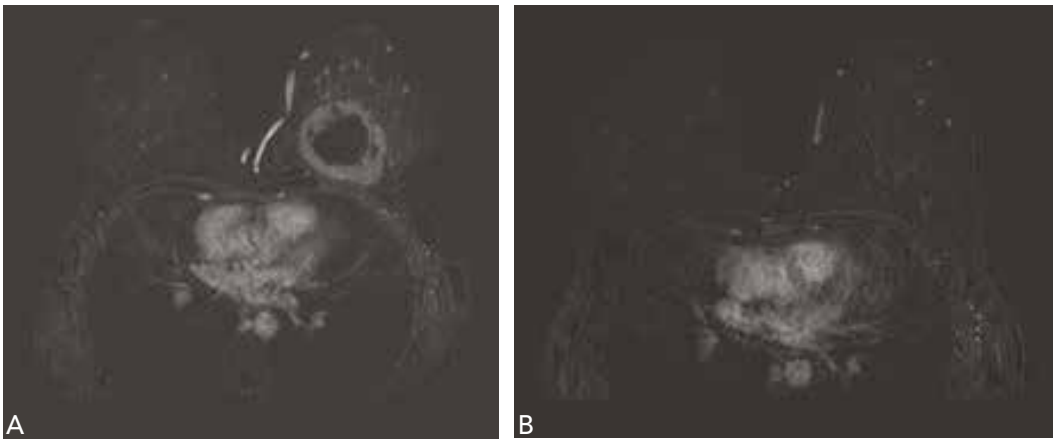


Figure 3.
A. Baseline MRI breast delineates a large necrotic mass (Triple-negative tumour) prior to neoadjuvant treatment.
B. There is no residual enhancement at site post-completion of treatment and pathological complete response has been confirmed histologically at surgery.



6. Where available, MRI staging may be considered for patients who may be candidates for accelerated (short, sharp and focussed) **partial breast irradiation** to facilitate mapping of tumour bed.

MANAGEMENT OF PATIENTS UNDERGOING NEOADJUVANT CHEMOTHERAPY

Pretreatment scans provide the most accurate nonsurgical measurements of disease extent. MRI assessment after the completion of treatment can be used to localise residual disease with any residual enhancement at the site of previous disease considered suspicious regardless of kinetics (Figure 3).

SCREENING – BREAST MRI IN HIGH-RISK SCREENING & DENSE BREASTS

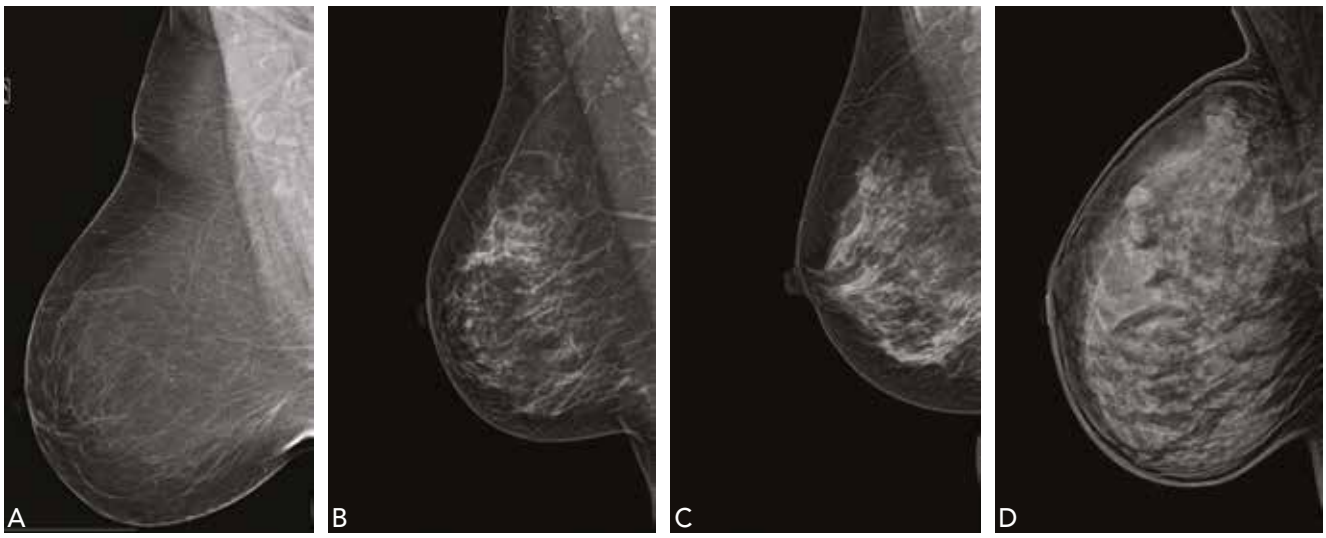
The vast majority of women with a family history of breast cancer do not have an identified genetic mutation. It is estimated that about 10% of breast cancers are clinically hereditary. At a molecular level, about 6% of breast cancer patients actually harbour pathogenic variants in *hereditary breast cancer genes*: half of these in BRCA1, BRCA2 and other high-risk genes and half in moderate risk genes (such as ATM, CHEK2).

Breast MRI screening in these patients is recommended commencing at circa 30 years of age. The following table summarises recommended intensified screening protocols.[7,8]

Pathogenic Variants	Lifetime Risk of Breast Cancer	Recommendations for Screening
BRCA1*	>60%	MRI screening from age 30 or 5 years younger than youngest family member with breast Ca at a 6-monthly interval
BRCA2	>60%	
PALB2	40-60%	Annual MRI from age 30 years or 5 years younger than youngest family member with breast Ca
PTEN	40%	
TP53	40%	
CDH1	40% (Lobular breast cancer)	Depending on availability, resources and local guidelines consider the following imaging in between MRI studies: In carriers 30-39 y of age – US +/- mammography In carriers > 40 y of age, mammography +/- US
STK11	40%	
ATM	25-30%	
CHEK2	25-30%	
BARD1	20%	
RAD51C	20%	Consider avoiding mammography in TP53 pathogenic variants
RAD51D	10%	

* Breast cancer in women with this pathogenic variant exhibits fast growth rate shortening 'lead time'

Figure 4. As per BIRADS descriptors of Breast density
A. Almost entirely fatty.
B. Scattered fibroglandular tissue.
C. Heterogeneously dense.
D. Extremely dense.



Childhood and young adult survivors of *Hodgkin's lymphoma* (HL) are at an increased risk (10-20% incidence by 40 years of age) of developing breast cancer secondary to chest-wall radiation exposure prior to the third decade of life. Incidence begins to rise approximately eight to ten years following HL treatment. Breast MRI screening in these women is recommended to commence at 25 years of age or 8 years after radiation treatment (whichever comes later).

Breast density i.e. the proportion of glandular component relative to fatty elements in the breast, is a recognised independent risk factor for breast cancer development. In women with largely adipose breasts, the sensitivity of mammographic screening reaches up to 90%. In women with *extremely dense breasts* this sensitivity decreases to less than 70%. Supplementary imaging may help improve performance of population-based screening. The European Society of Breast Imaging (EUSOBI) has acknowledged the merits of tackling this issue of the underdiagnosis faced by screening women with dense breasts with mammography (including Digital Breast Tomosynthesis) alone. Recommendations include:[9]

- Appropriately informing screening clients about their *individual breast density.*
- Supplementary screening is recommended in women with extremely dense breasts (Figure 4).
- This supplementary screening should be done preferably with MRI. EUSOBI recommends supplementary MRI screening in women aged 50-70 years with extremely dense breasts, preferably every 2-3 years.
- Where MRI screening is unavailable, sonography in combination with mammography may be used as an alternative.
- Emphasising the importance of *shared decision making* with clients throughout the screening experience.

IN WOMEN WITH EXTREMELY DENSE BREASTS THIS SENSITIVITY [OF MAMMOGRAPHIC SCREENING] DECREASES TO LESS THAN 70%. SUPPLEMENTARY IMAGING MAY HELP IMPROVE PERFORMANCE OF POPULATION-BASED SCREENING

Figure 5. Patient referred for MRI breasts with single-duct right-sided haemorrhagic nipple discharge and normal mammogram and ultrasound.
A. Elongated enhancing right retroareolar lesion demonstrated on MRI.
B. Subtle correlate identified sonographically cored and clipped with diagnosis of an intraductal papilloma confirmed histologically.

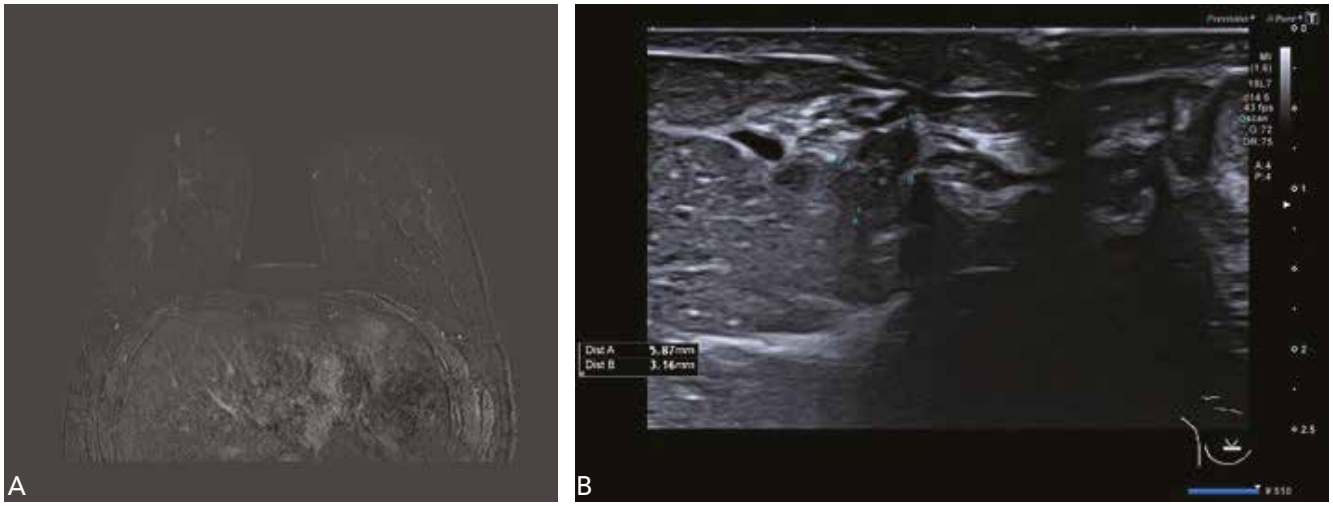
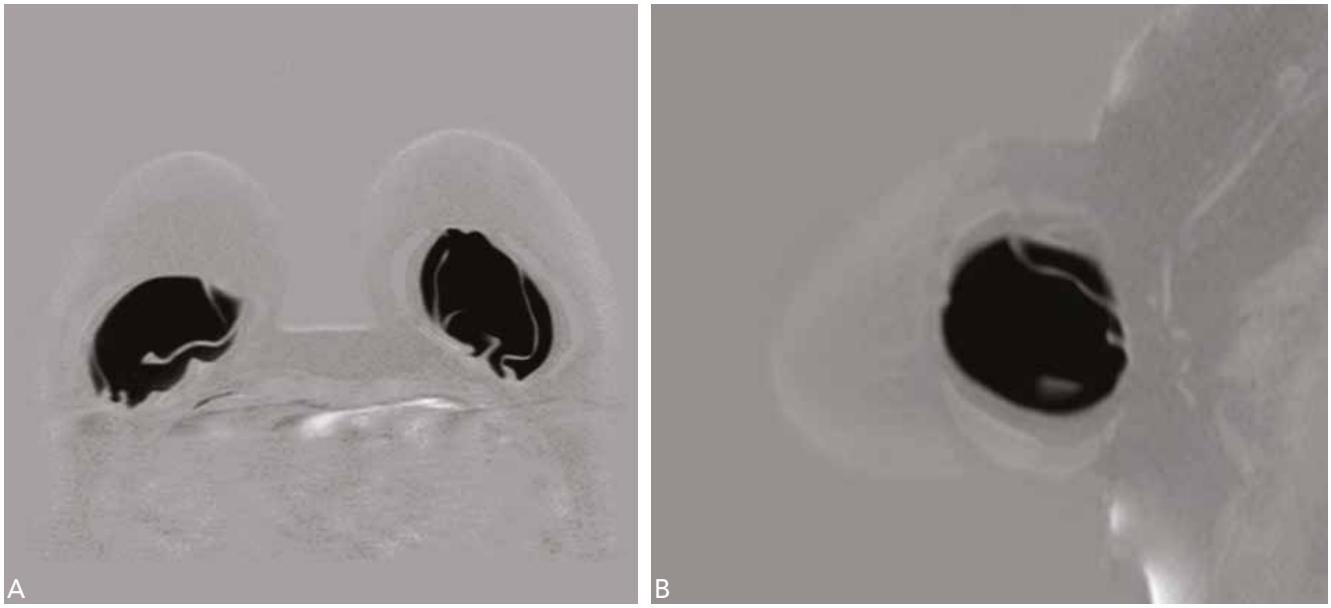


Figure 6. Silicon-only sequences in A. axial and B. sagittal planes illustrate subcapsular lines in keeping with a degree of intracapsular collapse.



BREAST MRI IS UNDENIABLY A MAJOR PART OF THE UP-TO-DATE MANAGEMENT AND WORKUP OF WOMEN WITH MANY BREAST CONDITIONS OR AT INCREASED RISK OF DEVELOPING BREAST CANCER

WORKUP OF SUSPICIOUS NIPPLE DISCHARGE

Breast MRI is recommended for individuals with suspicious nipple discharge – persistent, reproducible, spontaneous, unilateral/single duct clear or haemorrhagic nipple discharge – in the context of normal clinical and conventional imaging examinations.[5] Fluid may potentially be identified in dilated ducts as well as an enhancing mass (cancer or papilloma) (Figure 5).

BREAST IMPLANT INTEGRITY ASSESSMENT

MRI is the modality of choice for the assessment of implant integrity. MRI distinguishes silicon gel from fat, water, glandular tissue, and any other tissues in the breast based on their *unique MR relaxation properties* using specific pulse sequences. Silicon has a unique magnetic resonance frequency that allows for *silicon-selective sequences* to be performed – silicon's selective frequency accounts for the high accuracy and specificity seen with implant integrity MRI (Figure 6). Post-gadolinium sequences are not required in this particular scenario.[1]

CONCLUSION

Breast MRI is undeniably a major part of the up-to-date management and workup of women with many breast conditions or at increased risk of developing breast cancer. Inherent properties of varying lesions within the breast facilitate not just their identification but also characterisation. MRI findings may merit sampling – this may be performed at a second-look sonographic assessment or, as necessary, under MR guidance.

Through it all, the patient is priority and the importance of advising her with regards to why MR assessment is indicated, how scan is performed and potential outcomes such as identification of further disease cannot be overemphasised. Gathering the relevant information with subsequent discussion of findings at clinical, radiological and pathological levels results in optimisation of care recommendations, which can be provided to breast patients/screening clients, facilitating the shared decision process patients deserve and should now expect.

Having discussed the multiple indications for Breast MRI, improved accessibility to the modality, ever-developing technology and the use of shorter new sequences implies Breast MRI may be adopted for yet further uses in the near future – watch this space!

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DR MARIE ADRIENNE ZERAFA SIMLER, DR STEPHANIE MIFSUD

Neuraxial Anaesthesia in the Parturient with Multiple Sclerosis

ABSTRACT

Multiple Sclerosis (MS) is one of the most commonly acquired neurological diseases in young adults. Due to its pathological process, anaesthetic considerations in parturient women can be difficult and must include the safety of both the mother and foetus. This case report describes the management of pain relief during labour and subsequently a Category 2 caesarean section of a 30-year-old woman (pregnant for the first time or G1P0) with MS, with epidural anaesthesia. A multidisciplinary team approach, and early planning was essential for the success of this case. This case report indicates that epidural anaesthesia is safe in the parturient with MS during labour and that there is no association between epidural anaesthesia and relapse rates of MS in these individuals.

KEYWORDS

Multiple sclerosis, Epidural anaesthesia, Pregnancy

INTRODUCTION

Multiple Sclerosis (MS) is one of the most commonly acquired neurological diseases of the central nervous system (CNS), affecting young people.[1,2] It is an autoimmune disease which is characterised by inflammation and demyelination in the brain and spinal cord. MS affects women two to three times more than men[1-3] with the highest prevalence amongst young genetically susceptible individuals in the North of Scotland, Northern Europe, Northern United States, and Canada. Genome-wide associations studies have identified the human leukocyte antigen (HLA) gene cluster on chromosome 6p21 as the strongest locus for MS.[4] The average age of symptom onset is between 28 to 31 years. This has implications on significant life events, such as pregnancy, which can potentially become a real cause for concern in terms of the neurological, obstetric, and anaesthetic management throughout the course of pregnancy and the peripartum period.[4,5] This case was deemed important for dissemination because the choice of anaesthetic techniques, particularly spinal and epidural neuraxial anaesthesia in pregnant women with MS is still controversial and challenging.[1,3,6]

CASE PRESENTATION

We describe the management of pain relief during labour and subsequently a Category 2 caesarean section of a pregnant (pregnant for the first time or G1P0) 30-year-old women with MS, with epidural anaesthesia. The patient was in full remission throughout her pregnancy and was not on her regular MS medication as advised by her neurologist. An MRI performed during her third trimester showed stable appearance of her disease and no new lesions have been identified.

To ensure optimal anaesthetic management, multidisciplinary discussions involving anaesthetists, obstetricians and the patient's neurologist were undertaken, taking into consideration the patient's wishes for a normal vaginal delivery. The decision to proceed with an epidural anaesthetic technique was then discussed with the patient and it was agreed that this would provide both optimal pain management and a more favourable birthing experience.[7] An epidural was inserted uneventfully, early on during the first stage of labour to ensure that it was working appropriately in case of a category 1 caesarean section. Following the initial test dose of 3 ml of 0.25% bupivacaine and 6 ml of 0.125% bupivacaine were administered as a loading dose with good effect and no immediate or early complications. The patient spent 14 hours with the epidural catheter in situ, being administered a low-dose local anaesthetic and opiate infusion of 0.1% bupivacaine and 2 mcg/ml fentanyl at a rate of 8mls/hr into the epidural space as maintenance.

Low-concentration local anaesthetic mixtures were used to limit neuraxial dosing to the lowest dose possible in order to achieve adequate pain management in this patient with MS during labour and delivery as recommended by the literature.[1,5,8,9] This is due to the demyelinated neurones' increased susceptibility to the effects of local anaesthetics. Although high doses of local anaesthetics may increase the risk of relapse, stressful conditions such as surgery, delivery, and fatigue have been found to be more significant in increasing chances of MS

GENOME WIDE ASSOCIATIONS STUDIES HAVE IDENTIFIED THE HUMAN LEUKOCYTE ANTIGEN (HLA) GENE CLUSTER ON CHROMOSOME 6P21 AS THE STRONGEST LOCUS FOR MS

relapse.[2] It is therefore very difficult to distinguish between the effects of these stress-inducing factors and local anaesthetic drugs. However, epidural anaesthesia is known to reduce stress and fatigue during the peripartum period and thus, possibly mitigate the harmful effects of these factors.[6] In addition, with an epidural technique the concentration of local anaesthetic in contact with the spinal cord is 3 to 4 times lower than in spinal or subarachnoid anaesthesia, thus diminishing the neurotoxic potential.[9]

Eventually, the patient underwent a category 2 caesarean section due to failure to progress. A mixture of low-dose epidural anaesthetic, i.e. lidocaine 340 mg, adrenaline 0.1 mg and sodium bicarbonate 168 mg, was administered via the epidural catheter prior to caesarean section. The top-up worked with a good effect, achieving a sensory block up to the T5 dermatomes bilaterally. The patient underwent an uneventful category 2 caesarean with the successful use of the epidural catheter inserted early in the first stage of labour. This planned method of anaesthesia allowed the patient and her partner to see and hold their newborn as per the patient's wishes.

Postoperatively, it was agreed with the obstetricians that the patient should remain in central delivery suite for one-to-one monitoring overnight, with transfer to a normal obstetric ward the following morning if well. The patient was prescribed adequate pain relief, including paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and opiate patient-controlled analgesia (PCA) as per local protocol. The patient was reviewed in the days following her caesarean section with the anaesthetic team. She was pain-free, had sustained no complications following the epidural catheter insertion, and reported no new neurological symptoms of flare-ups of MS. She was also restarted on her MS medication immediately post-caesarean section by her neurologist. The patient was very satisfied with her anaesthetic care and was very pleased with the birthing experience and pain relief she was provided.

CONCLUSION

In conclusion, effective interspeciality communication and a multidisciplinary patient-centred approach, was of key importance in the management of this parturient with MS during labour and delivery of her child. Early planning was a key determinant in the success of this case, and regular communication and anaesthetic assessment of the patient throughout her labour was fundamental to ensure successful neuraxial anaesthesia and an optimal patient experience. This case report is in-keeping with the literary evidence which indicates that epidural anaesthesia is safe in the parturient with MS during labour and that there is no association between epidural anaesthesia and relapse rates of MS in these individuals.[6,10] It is hoped that this case report will encourage further research in the field of neuraxial anaesthesia in neurological diseases such as MS and improve family planning for these patients and their families.

ACKNOWLEDGEMENTS

This case report was published with the written consent of the patient.

The authors declare that they have no competing financial interest of personal relationships that could have appeared to influence the work reported in this case report.

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Opzelura is indicated for the treatment of non-segmental vitiligo with facial involvement in adults and adolescents from 12 years of age.[1]

Reference: 1. Opzelura SmPC.

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MR ADRIAN MIFSUD, DR MAXIMILLIAN AQUILINA

Towards Sustainable Ophthalmology:

An Analysis of Custom Packs used in Cataract Surgery to Reduce Waste and CO2 Emissions

KEYWORDS
Sustainability, Theatre, Ophthalmology

INTRODUCTION

Sustainability in healthcare is increasingly vital, particularly in operating rooms where significant waste and CO2 emissions are generated. The healthcare sector contributes to 4.4% of global greenhouse gas emissions, with operating rooms responsible for 71% of this due to disposable supplies.[1] Cataract surgery, a common procedure, heavily relies on disposable items, leading to substantial environmental impact. This study examines the custom cataract surgery pack used at Mater Dei Hospital, comparing it to the European Society of Cataract and Refractive Surgery (ESCRS) benchmark to identify potential improvements in sustainability practices.

PURPOSE

The purpose of this study is to examine the custom pack used at Mater Dei Hospital and compare it with the benchmark pack recommended by the ESCRS. The goal is to raise awareness and recommend practice changes if necessary.

METHODS

The custom pack used at Mater Dei Hospital in May 2024 was evaluated by reviewing the contents and inputting them into the Sustainability Index for Disposables in Cataract Surgery (SIDICS) calculator, which was recently published on the European Society of Cataract and Refractive Surgery (ESCRS) website. When products that were not exact matches were identified in the calculator, the closest available option was selected as an alternative.

RESULTS

In 2023 at Mater Dei Hospital, approximately 4203 custom packs for cataract packs were used. However, these are not solely used for cataract operations, but also for other types of ophthalmology surgeries such retinal surgery, glaucoma surgery and corneal surgery. 3933 of these packs were used specifically for cataract operations. The assessed custom pack uses 7.6 kg of CO2 equivalent per pack. The ESCRS benchmark pack uses 4.9 kg of CO2 equivalent per pack. Therefore, there is a potential for saving 2.7 kg of CO2 per pack, which would have amounted to 11,348 kg of CO2 in 2023.

Figure 1. Current custom pack used at Mater Dei Hospital.

Current Custom Pack	Size / Quantity	Current custom pack Carbon footprint (grams, CO2 Equivalent)
OR Gown Surgeon	XL	698.5
Or Gown Scrub Nurse	L	669.7
Body Drape with Pouch	157x254cm	2847.7
Back table cover	140x140cm	2495.8
Eye Shield	1	95.5
Eye Pad	3	17.1
Surgical Spears	10	3
Slit Knife	1	112.7
Sideport Knife	1	185.6
2ml Syringe	3	22
10ml Syringe	1	89
Cannula for Hydrodissection	2	12.1
Cystotome	1	18.3
Other Needles/Cannulas	3	12.2
Cataract pack overpack	1	230.4
Product List + Sticker	2	40.8
Total per pack		**7.6Kg**

Figure 2. ESCRS Benchmark Pack.

ESCRS Custom Pack	Size / Quantity	ESCRS custompack Carbon footprint (grams, CO2 Equivalent)
OR Gown Surgeon	L	669.7
Or Gown ScrubNurse	L	669.7
Body Drape with Pouch	100*120cm	856.9
Back table cover	110*140	1782.7
Gauze Swab	5	6.7
Stick Swab	2	22
Paper Towel/Operating room towel	1	91.3
Instrument Wipe	1	136.9
Slit Knife	1	112.7
Sideport Knife	1	185.6
Syringe 3ml	1	37.1
Syringe 5ml	1	36.4
Cannula for Hydrodissection	1	12.1
Cystotome	1	18.3
Cataract pack overpack (plastic)	1	230.4
Product List	1	77.5
Total per pack		**4.9Kg**

DISCUSSION

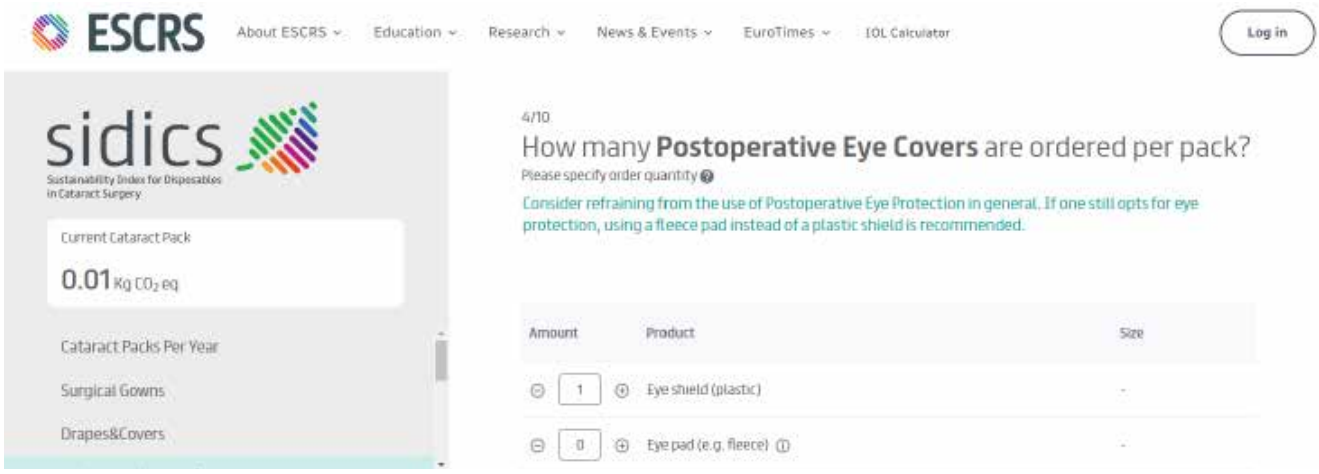
Cataract surgery is a common procedure that generates a significant amount of waste due to the use of single-use items such as drapes, gowns, and instruments. To prioritize sustainability, healthcare facilities are adopting more environmentally friendly practices such as using reusable options and reducing unnecessary waste to mitigate environmental impact.[1] One recent development at Mater Dei Hospital is the introduction of re\cycling bins for disposing of recyclable packaging waste. In keeping with this, studies have revealed that most ophthalmology practices could improve in reducing waste, travel, and carbon footprints.[2,3]

Cataract surgery has seen a shift towards disposable medical supplies in recent years.[4] This trend may be linked to concerns about prion diseases, which led to stricter (and more expensive) sterilization procedures for reusable instruments and surgical environments around 1996. However, the WHO stated in 2016 that there is no increased risk of infections during surgery when using appropriately sterilised reusable materials compared to disposables.[5]

Custom packs contain the necessary instruments and supplies for cataract surgery, tailored to the preferences and requirements of surgeons to reduce waste, and improve efficiency. However, it is important to note that not all ophthalmic surgeons use the same instruments found in the pack, and these packs may not be used exclusively for cataract surgery. By being aware of the impact that our choices have on the environment, we can make more informed decisions about the contents of our standard pack, reducing excess inventory and minimizing carbon dioxide (CO2) impact. These packs can also enhance efficiency and reduce surgical time, by ensuring that all the necessary items are readily available during surgery.

The SIDICS calculator helps assess the environmental impact of different cataract surgery packages. The calculator uses generic data to show the CO2 impact of the most common materials we use during surgery. The developers explain that the results should be interpreted as approximate estimates of environmental impact and not as absolute values. The SIDICS calculator estimates the environmental impact of different cataract surgery package configurations by analyzing data from three Austrian suppliers. This tool is meant to provide information and guidance but doesn't cover all possible product options. Consequently, the calculated results may be slightly inaccurate. It is important to consider that the contents of the ESCRS pack are only recommendations. As shown in the results section there are considerable differences in the number and type of items which have been deemed as the basic cataract set by the ESCRS. The selection of drape and gown sizes in cataract surgery remains subjective, determined by the surgeon's judgment. Key considerations during selection include surgeon comfort, ease of instrument manipulation within the draped field, and ensuring adequate patient and staff coverage.[6] Not using an eye shield has become common practice in many facilities as they have been found to offer no benefit on post-op recovery after uncomplicated cataract surgery, yet it is up to the operating surgeon to decide whether to use one or not.[7] The ESCRS acknowledges that doctors should use their own judgement when making decisions and the aim of the calculator is to provide insights for eco-conscious cataract surgery choices without dictating methods of practice.

Figure 3. Screenshot from the ESCRS website. This shows the webpage of the SIDICS calculator recommending against the use of an eye shield in the postoperative period.



After reviewing our current custom packs and comparing them to the ECSRS benchmark, we have identified a significant difference in the CO2 footprint. The benchmark indicates that there is room for improvement in our current packs. Our packs include surgical gowns, drapes, and covers, which are typically larger and have a higher environmental impact. Additionally, our current packs include a larger variety of fluid management items, eye shields and eye patches as well as variations in the number and sizes of syringes and cannulas compared to the ESCRS pack.

LIMITATIONS

We acknowledge that that the composition of custom packs utilized at Mater Dei Hospital during the calendar year 2023 may exhibit variations compared to those analyzed in May 2024. Such variations are attributable to the cyclical nature of procurement processes. However, they are usually similar with minimal alterations.

OUR RECOMMENDATIONS

- To review the current custom packs and following consultation with ophthalmologists and hospital management,
  - reduce the number of disposable items.
  - review the size of surgical drapes and surgeon gowns currently in use.
- To review and implement practices changes by increasing recycling and using more eco-friendly materials.

CONCLUSION

A survey among ESCRS member cataract surgeons reveals a strong consensus on the need to reduce operating room waste and a willingness to reuse surgical supplies and medications, reflecting a global concern for sustainability in healthcare. It also found that most surgeons preferred more reusable supplies and device options including reusable instruments.[8] By carefully reviewing the current custom pack and ensuring that the European benchmark is considered when ordering new custom packs, we could potentially save up to 2.7 kg of CO2 per pack. This could be a starting point for a more sustainable practice at Mater Dei Hospital after further consideration and analysis.

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MR MARK BRINCAT, MS MARIA PETRA AGIUS

Fertility preservation strategies in early-stage cervical cancer

ABSTRACT

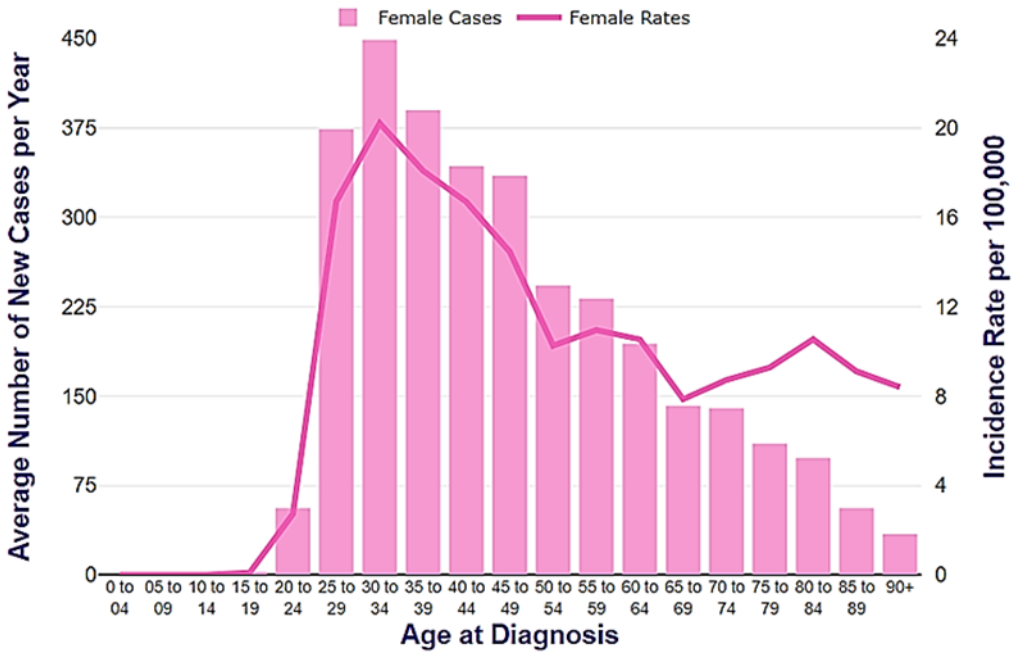
Early-stage cervical cancer poses unique challenges for women of reproductive age who wish to preserve their fertility. This article provides a comprehensive overview of fertility-preserving treatment strategies, focusing on surgical options which spare the uterus, such as conization and trachelectomy, as well as ovarian transposition. It examines the criteria for selecting appropriate surgical candidates, the role of accurate clinico-radiological staging, and the importance of thorough counselling by an experienced multidisciplinary team. Additionally, it explores assisted reproductive technologies that support fertility preservation including oocyte, embryo, and ovarian tissue cryopreservation. By emphasizing individualized treatment plans, we underscore the necessity of balancing long-term oncological outcomes with fertility preservation to enhance the quality of life for cervical cancer survivors.

BACKGROUND

Cervical carcinoma is the fourth most common cancer in females globally. Human Papilloma Virus (HPV) is the main culprit in its pathogenesis and is also associated with anogenital, oral and laryngeal malignancies.[1] HPV persistence, immunosuppression, smoking and co-existing infections have been associated with higher risk of progression from pre-malignant lesions to squamous cell or adenocarcinoma. Screening using cervical cytology 'pap smears' or more recently using HPV-triaging, detects 90% of cancers and pre-malignant lesions and is an essential prevention strategy combined with an HPV immunization programme (introduced in 2013).[2]

Cervical cancer in Malta has a crude annual incidence rate of 5.91 per 100,000.[3] In approximately 80% of cases, the histological subtype is squamous cell carcinoma, followed by endocervical adenocarcinoma, which tends to be associated with worse prognosis.[4]

Figure 1. Average number of new cervical cancer cases per year and age-specific incidence rates per 100,000, UK, 2016-2018.[5]



The age group most frequently diagnosed with cervical cancer is 30-34 years, which is the age range at which most women deliver their first child in Europe, especially in an era where childbearing is delayed past 30 years. (Figure 1).[5] Since loss of fertility and premature ovarian insufficiency may be an undesired complication of cancer treatment, fertility-sparing surgery and fertility preservation options have evolved drastically and are considered a public health issue. This article provides an overview of the strategies one can employ when treating cervical cancer to preserve fertility without compromising oncological outcomes.

WHAT IS 'EARLY-STAGE' DISEASE?

Cervical malignancies are staged according to the 2018 FIGO (International Federation of Gynecology and Obstetrics) staging. Staging at diagnosis is clinico-radiological, with a speculum and bimanual examination, and cross-sectional imaging. PET-CT plays a role when locally advanced disease is suspected (Stage 1B3 and higher) and primary non-surgical treatment is anticipated. Early-stage disease includes tumours that are less than 4cm in size, are confined to the cervix and with no associated locoregional or distant spread.[6]

Fertility-sparing surgical techniques for cervical cancer are an option for patients with good prognostic factors and disease amenable to curative-intent surgery without adjuvant therapy.[7] Oncologic safety can be assessed in terms of clinico-pathologic risk factors for recurrence.[8] These include tumour size, depth of stromal invasion, presence of lymphovascular space invasion (LVSI), lymph node and parametrial involvement and the feasibility of achieving tumour-free margins.

Early Stage 1A cancers are in the majority of cases treated with local excision, with or without nodal staging, allowing fertility preservation. Cases diagnosed beyond Stage 1A, particularly in the presence of high-risk factors such as lymphovascular space invasion, may necessitate a more radical surgical approach. The standard of care for Stage 1B1 (<2cm) and 1B2 (≥2 and <4cm) cases has traditionally involved a curative-intent radical hysterectomy, with resection of parametrial tissue, an upper vaginal cuff and pelvic lymph node staging. In a proportion of these patients, through careful decision-making, we can offer safe oncological management without precluding future pregnancy.

A study by Matsuo et al[9] showed that patients with tumors measuring less than 2cm have a two-fold increase in survival compared with tumors measuring between 2cm and 4cm, supporting the revision to 2009 FIGO Stage 1B categories. The revised staging system has facilitated patient triaging and treatment stratification in this aspect by dividing the old 1B1 category (<4cm) into two new groups - the 1B1 category (up to 2cm) and 1B2 category (≥2 and <4cm).[10,11] A fertility-sparing approach with a tumour size of >2 cm is associated with an increased risk of recurrence (up to 42.9%) and nodal metastasis, regardless of the surgical approach adopted.[12] Therefore, at present, a fertility-sparing approach in this situation is only acceptable in the setting of a clinical trial due to the potential oncological sequalae.

FERTILITY PRESERVING SURGICAL OPTIONS

To be eligible for fertility-sparing management of cervical cancer, two main criteria must be met; 1) the patient's desire for, and likelihood of, fertility must be sufficiently high, and 2) oncologic safety must be acceptable. Eligibility for fertility-sparing surgery should also reflect local legislational age-related eligibility

Table 1. Differences between the 2009 and 2018 FIGO early-stage cervical cancer staging.[8]

FIGO 2009	FIGO 2018
Stage 1A - Invasive carcinoma with maximum depth of invasion <5mm and no wider than 7mm	Stage 1A - Invasive carcinoma with maximum depth of invasion <5mm
1A1 Measured depth of stromal invasion <3mm and <7mm in width	1A1 Measured depth of stromal invasion <3mm
1A2 Measured depth of stromal invasion ≥3mm and <5mm, and <7mm in width	1A2 Measured depth of stromal invasion ≥3mm and <5mm
Stage 1B - Invasive carcinoma with measured deepest invasion ≥5mm, or horizontal dimension >7mm, limited to cervix uteri	Stage 1B - Invasive carcinoma with measured deepest invasion ≥5mm, limited to cervix uteri
1B1 <4cm in greatest dimension	1B1 <2cm in greatest dimension
	1B2 ≥2 and <4cm in greatest dimension
1B2 ≥4cm in greatest dimension	1B3 ≥4cm in greatest dimension

policies for assisted reproductive technologies. Other parenting options should also be discussed if deemed appropriate for the patient. Patient selection is key - it is essential that treatment strategies avoid combining radical surgery and radiotherapy because of the higher morbidity induced by the dual-modality treatment.

1. LOOP EXCISION TREATMENT / CONIZATION

Stage 1A1 cervical cancer should be diagnosed through loop excision (Figure 2) or conization to establish a microscopic assessment of depth, tumoral extension, margins, and LVSI before planning any further treatment. In these patients, treatment with loop excision or conization with free margins can be considered definitive, as hysterectomy does not improve the outcome. Nodal metastasis in this cohort is very low, however staging may be considered with LVSI.[6] Conization (with clear margins) alone or simple hysterectomy is also an adequate treatment for patients with Stage 1A2 disease. Surgical pelvic node staging can be considered in LVSI-negative patients but should be performed in LVSI-positive patients.[6]

2. TRACHELECTOMY

Trachelectomy was first described by Dargent in 1987, and consists of the removal of the cervix and vaginal margins while leaving the uterine body in situ.[14] Since this original description, the procedure has been modified and is currently performed via the vaginal, abdominal, or minimally invasive approaches, based on the surgeon's preference and experience.[15] An isthmic cerclage stitch is routinely applied during this procedure to reduce the risk of future premature delivery.

Strict criteria must be met in order to confirm eligibility for trachelectomy: 1) desire to preserve fertility, 2) tumour size <2 cm, 3) FIGO Stage IA–IB1, 4) absence of distant metastasis on imaging, and 5) absence of unfavorable histologic types (e.g. neuroendocrine tumors). Several studies found this procedure to have comparable survival and recurrence rates to radical hysterectomy, making it a safe alternative for patients wishing to preserve fertility.[16,17] The risk of recurrence following trachelectomy is in the region of 5%, which is non-inferior to that seen following radical hysterectomy. After a trachelectomy, the risk of the patient eventually still requiring treatment that is fertility-sacrificing (such as radiotherapy for microscopically positive pelvic nodes or positive margins) is in the region of 11%.[18]

Trials such as CONTESSA are assessing whether neo-adjuvant chemotherapy is effective at reducing the size of the tumor in patients who are not primarily eligible for fertility preserving surgery, and whether this could enable fertility-sparing surgery at a later stage without compromising oncologic outcome.[19]

PREGNANCY AFTER CERVICAL CANCER TREATMENT

Cervical cancer treatment has a significant impact on the obstetric risks of established pregnancies.[20] This primarily relates to the increased risks following surgery, but it also relates to risks associated with chemotherapy and pelvic irradiation. These could form part of primary non-surgical treatment, or could be post-operative if adjuvant treatment is indicated to reduce recurrence risk as per Sedlis criteria. [21]

Contraception is advised for 6 months after trachelectomy, in view of data showing that conceiving within 2–3 months of a conization procedure is associated with an even higher risk of preterm labour.[22] The post-operative pregnancy rate is the highest with the vaginal approach (37.8%).[15] Strategies to help reduce the risk of preterm labour include the transfer of a single-embryo during ART, regular urinalysis for asymptomatic bacteriuria, and screening and treatment of vaginal infections. The neo-cervical (isthmic) length

Figure 2. Large loop excision of the transformation zone (LLETZ).[13]

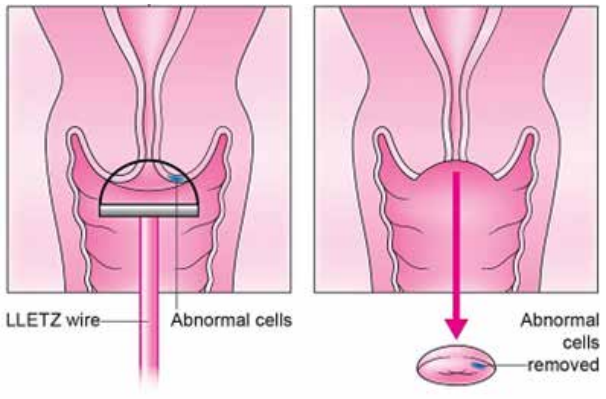
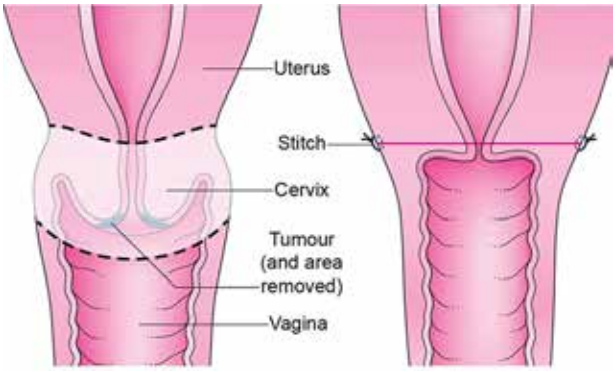


Figure 2. Trachelectomy procedure with isthmic cerclage.[13]



should be monitored routinely by ultrasound and corticosteroids should be considered to improve fetal lung maturity after 24 weeks of gestation if any signs of preterm labour are evident. Micronized vaginal progesterone should be prescribed from 12-36 weeks gestation.[23] Delivery should be planned at around 37 weeks gestation by elective cesarean section, or earlier if chorioamnionitis is suspected, especially in the context of membrane rupture.[24]

Pregnancies after chemotherapy are associated with increased risk of miscarriage, preterm labour and growth restriction, especially if pregnancy occurs within one year of completion of chemotherapy.[25,26] The effects of radiotherapy depend on the intensity of radiotherapy and the age of the patient at the time of radiotherapy administration; a higher risk of preterm labour, growth restriction and placental abnormalities have been reported. Pregnancy is contra-indicated in women who were exposed to >45Gy of radiation to their uterus, and this is often the case with non-surgically treated cervical cancer.[27]

THE ROLE OF THE FERTILITY TEAM

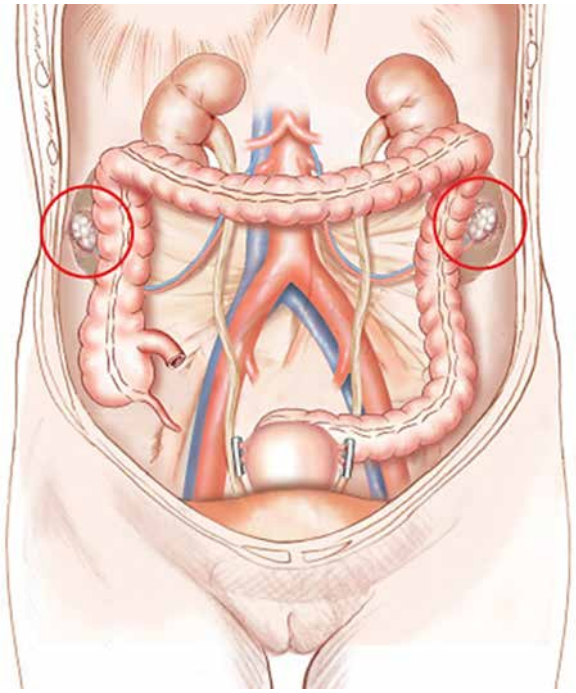
When fertility-sparing surgical options are available, the main input of the fertility team is during pre-operative counselling relating to the realistic risk of future pregnancy based on the planned treatment, age and ovarian reserve as well as on potential ART techniques that may need to be utilized.[28]

When fertility-sparing surgical options are not available or not desired by the patient, fertility preservation options can be considered after thorough counselling by a fertility specialist. The approach to such options relates to the urgency to start cancer treatment.

If no or very little time is available i.e. less than 2 weeks, the patient can be offered:

- **Ovarian transposition.** This is a procedure that reduces the radiotherapy-induced damage on the ovaries by displacing them away from the radiation field (Figure 3). This may be performed laparoscopically prior to chemo-radiotherapy, or can be performed via laparotomy as part of an initial radical surgical approach that would include ovarian preservation.[29] However, due to disruption of the adnexal anatomy (in particular the fallopian tubes), the chances of a spontaneous pregnancy are still limited and makes trans-vaginal oocyte retrieval more challenging.[30] This also reduces the risk of premature menopause and has a variable success rate of 44-85%.[29]
- **Ovarian tissue cryopreservation** involves removal and freezing of ovarian tissue cortex. The success rate of this procedure depends on ovarian reserve and can be performed at any stage of the cycle and even after chemotherapy has started. A small area of the tissue retrieved should be sent for histopathological analysis to exclude micro-metastases to the ovary especially in cervical adenocarcinoma sub-type.[32] This tissue can be later transplanted back into the pelvic peritoneum using sutures or fibrin glue using minimally invasive surgery.[33] This procedure is associated with a spontaneous pregnancy rate of 46%[34] and if this is not achieved, ovarian hyperstimulation with gonadotropins and In Vitro Fertilisation/Intra-Cytoplasmic Sperm Injection (IVF/ICSI) can be attempted.[35] The replacement of ovarian tissue can also provide physiological oestradiol and avoid the need for hormone replacement therapy.
- **GnRH analogues** that cause pituitary down-regulation and ovarian suppression, reducing the radiotherapy and chemotherapy-induced gonadotoxicity on the ovaries, and reducing the risk of ovarian failure.[36]

Figure 3. The ovaries sited outside the radiotherapy field high up in the paracolic regions following an ovarian transposition procedure.[31]



The following can be offered if cancer treatment can be delayed by around 2 weeks:

- **Oocyte cryopreservation.** This can be performed at any stage of the cycle, referred to as random-start stimulation. The number of oocytes collected is proportional to the patient's age (patients <36 years of age achieve better results) and serum anti-

müllerian hormone (AMH).[37] Unfertilized oocytes can be cryopreserved and later on thawed and fertilised with a survival rate of around 80-90% depending on the oocyte quality and laboratory cryopreservation and thawing expertise. Oocytes can also be fertilised and cultured to the blastocyst stage. In this case, the survival rate after thawing is around 97%.[38] Prior to such a decision the patient needs to be counselled regarding her prognosis, her own personal preferences (since the fate of such embryos are not under her sole control) and the legal framework of the country.

CONCLUSION

Fertility preservation techniques represent a critical advancement in the management of early cervical cancer, offering hope for women who wish to retain their reproductive capabilities post-treatment. As early detection methods improve and the survival rates for cervical cancer continue to rise, the focus on quality of life, including fertility, becomes increasingly significant. Striking the fine balance between oncological risk and fertility preservation in early-stage disease requires careful counselling by experienced healthcare professionals in this field. Such a decision to offer this treatment should be taken within a multidisciplinary team involving a surgical gynae-oncologist, a clinical oncologist, a fertility specialist and a psychologist amongst other professionals. The integration of fertility preservation into the treatment paradigm for early cervical cancer reflects a broader commitment to enhancing survivorship and quality of life for women facing this diagnosis.

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