



# NewsLetter

Vol. XXIV | No.6 | Price: 50 Paisa

## EDITORIAL

### LEARNING TO LIVE WITH COVID AND CANCER

The world has changed in 100 days. It is hard to imagine that the disease which started as undiagnosed pneumonias in Wuhan in Dec 2019 would sweep across the world and bring mankind to its knees. Even now, the global coronavirus pandemic continues to escalate at a rapid pace incapacitating medical facilities and creating significant challenges worldwide. As the data and research on COVID-19 is still fairly new, there is so much that is left unknown, particularly with regard to recovery, immunization, transmission, and links with other existing conditions.

The main modes of SARS-CoV-2 transmission are through respiratory droplets and contact, whereas airborne transmission may be possible for situations in which aerosols are generated, such as endotracheal intubation and during bronchoscopy. The mean incubation period in patients is approximately 4 to 5.2 days and the mean serial interval, or time between the onset of symptoms in one individual and onset in a serial individual, is 7.5 days

Coronavirus symptoms can vary from mild to severe illness and death. Many patients could be asymptomatic. Fever, cough and shortness of breath are the usual symptoms which may appear 2-14 days after exposure. Recent reports suggest that approximately 60% to 90% of patients present with fever, 55% to 70% with cough, and 33% with dyspnea. Other symptoms, which includes nausea, vomiting, and diarrhea, myalgia, fatigue, headache, sore throat, and new-onset loss of taste or smell were observed in less than 5% of patients. Approximately 15% to 20% of patients will develop severe symptoms and may require hospitalization and intensive care. Severe complications may include bilateral pneumonia acute respiratory distress syndrome and multiorgan failure. Emerging data indicate that vascular inflammation can result in diffuse microangiopathy with thrombosis, which contributes to multiorgan failure.

According to WHO and Centers for Disease Control and Prevention (CDC), the preferred current diagnostic method is the detection of SARS-CoV-2 nucleic acid in patient specimens. Appropriate samples include the upper airways (pharyngeal swabs, nasal swabs, nasopharyngeal secretions), the lower airways (sputum, bronchoalveolar lavage fluid specimens). Sputum and other lower respiratory tract specimens have a high positive rate of nucleic acids. Serologic tests are currently being developed.

Typical chest radiographic features of COVID-19 patients include consolidation with limited cases of pleural effusion. The Radiological Society of North America in its consensus statement classifies CT findings of COVID-19 pneumonia into typical, indeterminate, atypical appearances, and negative for pneumonia. The typical CT appearances specific for COVID-19 pneumonia is listed as peripheral, bilateral ground-glass opacities (GGOs) with or without consolidation. Atypical CT findings are only seen in a small minority of patients and should raise concern for superimposed bacterial pneumonia or other differential diagnoses.

There's no specific treatment for COVID-19. Patients who get a mild case need care to ease their symptoms, like rest, fluids, and fever control. For moderate cases, antiviral drugs like Remdesivir have been tried with some success. Dexamethasone in a study was also shown to be efficacious in reducing severity and complications of Covid infection. In severe cases, patients may need mechanical ventilation. Novel approaches like plasma therapy, tocilizumab, Low dose Radiotherapy to lung have been tried but remain experimental.

**Covid and Lung Cancer:** Covid pandemic has been a double trouble for cancer patients. Cancer patients are in a dilemma to choose between continuing cancer treatment and risking themselves to infection with Covid or staying at home while watching the cancer progress silently but surely. The patients and Oncologists are in an unenviable position to choose between Scylla and Charybdis. Lung cancer patients, especially those with reduced lung function and cardiopulmonary comorbidities are more likely to have increased risk and mortality from coronavirus disease 2019.

**How has Covid changed the treatment of Lung cancer:** There are challenges in the management of a patient with lung cancer given the similarities in radiologic findings, respiratory symptoms, and the presence of underlying immunosuppression. In early stage lung cancers an important issue is to decide whether to delay resection or not. Guidance from CDC and most professional societies indicates that elective surgeries should be rescheduled if possible. The American Society of Clinical Oncology recommended that clinicians and patients need to make individual determinations on the basis of potential harms caused by delaying needed cancer-related resection. However Surgical delays should generally not be more than 6 to 8 weeks. Neoadjuvant therapy is recommended for appropriate patients to mitigate any deleterious effects from postponing surgical intervention for situations in which surgical services are overwhelmed.

(Continued on Page No. 4<sup>th</sup>)

# ROLE OF SENTINEL LYMPH NODE IN CARCINOMA ENDOMETRIUM

## Introduction

Sentinel lymph node dissection is a relatively recent alternative staging technique in endometrial cancer that allows assessment of pelvic/para-aortic lymph nodes, alleviating the need for a complete systematic lymphadenectomy. This has led to a substantial decrease in the morbidities such as lymphedema, lymphocysts, cellulitis and damage to nearby nerves associated with systematic lymphadenectomy and has led to the detection of nodes in unusual nodal basins.

## Historical Perspective

French gynecologists, Leveuf and Godard, in the early twentieth century studied the lymphatic anatomy of the cervix by injecting Gerotti blue into the cervixes of neonatal cadavers. They found that the dye drained a lymph node found in the obturator space or at the bifurcation of the iliac vessels. They called it the **principal lymph node**. The concept of sentinel lymph node was formally introduced in 1960 by Ernest Gould while working on parotid gland cancer. But it was not until two decades later that Ramon Cabanas succeeded in mapping the sentinel lymph node in a case of penile cancer. The first gynecological cancer in which this technique was successfully established was in carcinoma vulva. The concept of SLN mapping in endometrial cancer was introduced by Burke in 1996 from the MD Anderson Cancer Center.

## Current State of Sentinel Lymph Node Evaluation in Endometrial Cancers

The primary objective of SLN mapping in endometrial cancer is to identify the lymph nodes most at risk for metastasis in order to limit complete lymphadenectomy procedures and their associated morbidities. GOG 33 demonstrated an overall risk of metastasis in pelvic and aortic lymph nodes of 9% and 6%, respectively, well-differentiated tumors had a risk of 3% and 2%, and tumor confined to the endometrium conferred an even lower risk of metastasis at 1%.

SLN mapping with ultra-staging may increase the detection of lymph node metastasis with low false-negative rates in women with apparent uterine-confined disease. With the initial studies of SLN mapping by Abu-Rustum *et al*, a low false-negative rate was demonstrated. The same investigators described a learning curve with an increase in SLN detection from 77% to 94% ( $p=0.03$ ) following a 30-case experience. Enhanced pathologic analysis with serial sectioning and IHC increased the detection of metastasis by approximately two-fold compared to routine H&E findings in patients undergoing SLN mapping, largely through the detection of micrometastases and ITCs that were not identified on the initial H&E examinations.

## Technique of Lymphatic Mapping

Conventionally, lymph node mapping has been done using technetium-99m (99mTc) radiolabeled colloid injections and Blue-colored dyes like 1% isosulfan blue and 1% methylene blue. The use of indocyanine green (ICG) with an infrared camera (with or without a colored dye) has replaced use of 99m Tc in many practices. Retrospective data suggest that blue dye alone (either isosulfan blue or methylene blue) is inferior to ICG alone in detection of sentinel lymph nodes, with combined blue dye and ICG having the highest rate of SLND detection.

At RGCIRC we use ICG for lymphatic mapping, 2-4 mL is injected using a 27-gauge needle/ spinal needle/ Potocky type needle into the superficial (1-3 mm) and deep (1-2cm) cervical stroma at the 3 and 9 o'clock position prior to hysterectomy.

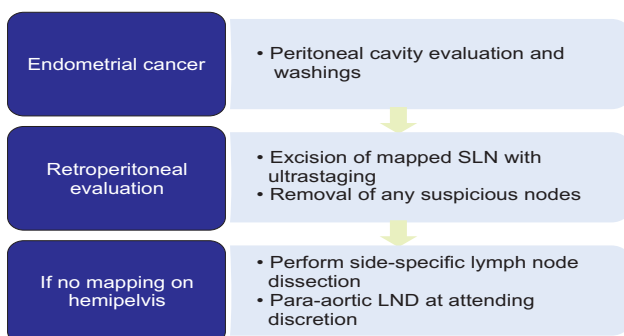
Following injection of the mapping product into the cervix, optimal detection of the ICG will occur between 15 and 60 minutes. Successful mapping of a hemipelvis is defined by observing a channel leading from the cervix directly to at least one candidate lymph node. Common iliac or aortic sentinel lymph nodes are also dissected if present. Identified sentinel lymph nodes as well as any suspicious nodes are then retrieved and sent for pathologic evaluation. If either hemipelvis does not map, then a side-specific pelvic, common iliac and internal iliac lymph node dissection is done.

Techniques of lymphatic mapping such as fundal injection or hysteroscopic injection have not been shown to have the convenience or the sensitivity for detection of sentinel lymph nodes, though hysteroscopic injection may be associated with an increased detection of aortic sentinel lymph nodes.

The rationale for using the cervical injection includes the following:

1. The cervix is easily accessible
2. The cervix in women with endometrial cancer is rarely distorted or scarred from prior procedures such as conization
3. The main lymphatic drainage of the uterus is from the parametria
4. Uterine fundal serosal mapping does not reflect the parametrial lymphatic drainage of the uterus

The main argument against the cervical injection is that it has a lower paraaortic detection rate, but as is well documented, when the pelvic lymph nodes are negative for metastasis, disease is unlikely to be found in the paraaortic nodes, and to date there has been no definitive association between paraaortic nodal assessment and improved overall survival.



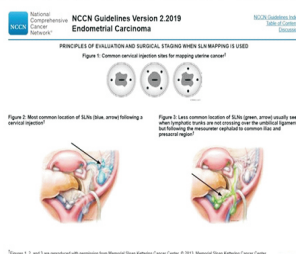
The key point to a successful SLN mapping is the adherence to the SLN algorithm, which requires the performance of the side specific nodal dissection in cases of failed mapping and removal of any suspicious and grossly enlarged nodes regardless of mapping.

## Pathological Assessment of SLN

“Ultrastaging” refers to the utilization of enhanced pathology techniques, to increase the detection of malignant cells in SLNs. The SLN ultrastaging protocol varies among institutions. Standardization of the pathologic assessment of removed SLND is critical to the correct use of this technique. Sentinel lymph node ultrastaging has two components:

1. Serial sectioning with review of multiple H&E stained slides, and
2. Cytokeratin IHC staining

## Sentinel lymphadenectomy : The Method



Sentinel lymph nodes are generally cut at 3 mm intervals, in a bread-loaf fashion, or bivalve if less than 1.5 cm in any dimension. Two paraffin-embedded slides are created from each section, each 50 micrometers apart. One slide is generally stained for hematoxylin and eosin (H&E) and the other is reserved for immunohistochemistry staining. If no metastatic disease is identified on the first H&E slide, the reserved slide is generally stained for cytokeratin AE1 and AE3.

Lymph nodes with isolated tumor cells should be clearly reported. When isolated tumor cells are detected in the absence of macro-metastasis and micro-metastasis, the lymph node stage is designated pN0(i+). Whether these should be included in FIGO stage III remains to be determined.

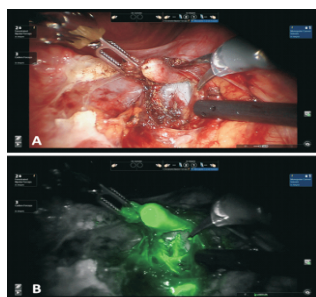
### Advantages of Sentinel Lymph Node Dissection

1. Decreased morbidity as compared to conventional lymphadenectomy
2. Unusual basins of drainage are identified

3. Ultra-staging detects an additional 8% positive nodes in the SLN in endometrial carcinomas with any degree of myo-invasion

Further studies are needed to confirm that utilization of sentinel node biopsy reduces lower extremity lymphedema, particularly given the number of patients ultimately requiring full LND.

Additionally, the populations in which lymphatic mapping and SLND are appropriate are being evaluated. While initially utilized in patients at low risk for lymph node metastasis (with a complete LND in those at higher risk), many centers have moved to utilizing SLND in all patients, with selective complete LND in specific circumstances.



### Conclusion

If a selective LND strategy is utilized to determine the management of a non-mapping hemipelvis, fewer than 10 percent of patients will require a complete pelvic LND without compromising the ability to detect metastatic disease in the lymph nodes.

SLN mapping is gradually becoming the standard of care for surgical staging in many institutions. The major factors to successful SLN mapping include the surgeon's experience (30 procedures or more) and adherence to the SLN algorithm published in 2012 and listed in NCCN guidelines since 2014.

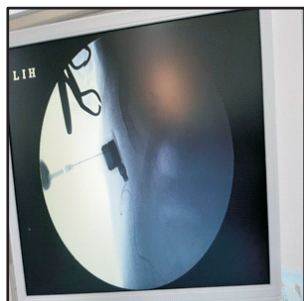
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### EPIDURAL PUMP IMPLANTATION FOR REFRACTORY CANCER PAIN MANAGEMENT: ROLE OF INTERVENTIONAL PAIN MANAGEMENT

WHO pain management ladder has been the mainstay of cancer pain management. Apart from pharmacotherapy that gives satisfactory pain relief in 75% of the cases, there are refractory cancer pain cases which need interventions for further pain relief. There are cases where an Interventional Pain Management expert has to think and perform some advanced implantable treatment techniques (a tunneled percutaneous catheter which is connected either to an external pump or is a totally implanted system with drug reservoir) where sympathetic blocks have been repeated multiple times and the patient still experiences pain. Such a case of pancreatic malignancy pain was managed successfully at Rajiv Gandhi Cancer Institute, Niti Bagh where we implanted an epidural catheter that was connected to a tunneled percutaneous port for drug administration.

A 60 year old patient of Carcinoma pancreas with liver metastasis was referred to Pain Clinic for treatment of severe pain (VAS 7/10). He was first managed conservatively using NSAIDs (diclofenac sustained release 100 mg once daily for 5 days) and anti-depressant Duloxetine 20 mg at night. Due to severe pain intensity, morphine sustained release tablets 30 mg twice daily were started after titration of the dose with immediate release preparations. Because of the increasing doses of opioids and their side-effects (constipation and somnolence), we performed trans-aortic celiac plexus neurolysis after a diagnostic injection, followed by bilateral splanchnic radiofrequency ablation. These procedures provided pain relief for a period of 8-9 months. In due course of time, patient had progression of disease and the opioid (oral morphine) dose increased to more than 100 mg/day. Because of the bothersome side-effects, epidural pump implantation was planned. Intrathecal pump implantation could not be done due to financial constraints. After getting good pain relief (> 50 percent) with gradually escalation of epidural morphine test dose to 6 mg, patient was implanted with a Vygon mini-sitimplant. It was introduced from L2-L3 intervertebral space (IVS) and the tip of catheter was kept at T9-T10 IVS. The tip was confirmed with dye spread that went up to T8-T9 IVS. The catheter was tunneled under the skin and the port reservoir was placed in a sub-costal pocket. It was then connected to Dosifuser epidural pump with markings 1 to 7 (0.1 percent ropivacaine with 10 mg morphine in 250 ml) via butterfly needle skin started at 3 ml/hour. Patient was advised to increase the dose in case of breakthrough pain episodes. Pump refilling is being done from time to time. Oral opioids were stopped, psychological counseling continued, anti-emetics/proton pump inhibitors/anxiolytics started and the patient was kept on palliative treatment.



Interventional pain management is gradually becoming an indispensable part of cancer pain management. A combination of pharmacological and interventional measures would give better symptomatic relief to patients with lesser adverse effects. In this case, we used a cheaper and affordable alternative to intrathecal pump implantation. Precautions with the pump and dosing instructions were carefully explained and closely monitored on follow up.

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Date of Printing: 25<sup>th</sup> June 2020

Date of Publishing: 30<sup>th</sup> June 2020

Posted at: Ashok Vihar, Head Post Office, Delhi - 110052

Register with Registrar of Newspaper Under No.68797/98

Postal Department Registration No. DL(N)/004/2018-20

Licensed to Post without Prepayment Under No.: "U"(DN)-162/2020

Adjuvant therapy is not recommended for stage I NSCLC patients as per standard of care practice. But in case of inability to start adjuvant cytotoxic chemotherapy wherever indicated, adjuvant EGFR tyrosine kinase inhibitor (TKI) therapy could be considered for *EGFR* mutation-positive NSCLC. For radiotherapy an alternative approach is the use of hypofractionation to decrease the number of radiotherapy fractions if appropriate.

For advanced diseases Systemic therapies associated with a reduced risk of myelosuppression, shorter treatment time, and lower frequency of treatment visits are recommended. Therapies with three weekly schedule rather than therapies with frequent visits such as daily or weekly schedules should be preferred. The use of granulocyte-colony-stimulating factor (G-CSF) should be strongly encouraged as prophylaxis for early secondary prevention of neutropenia, as appropriate. For patients with oncogene-driven NSCLC who are treated with a TKI, treatment can continue as prescribed. Follow-up evaluation through telemedicine is encouraged when possible. Response evaluation visits can be delayed, and CT scans are only advised in patients who are suspected of symptomatic progression.

To conclude, the world has changed in last 100 days. The rapid onset of the COVID-19 pandemic requires careful consideration of urgent decisions to treat lung cancer by oncologists. However, we must remember not to panic but to live with corona virus. The New Normal of cancer treatment entails discussion with patients, their care givers and Oncologists in a new way keeping the prevailing situation in mind and not compromising on the efficacy of anti-cancer treatment.

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Printed and Published by Mr. Pramod Maheshwari on behalf of Indraprastha Cancer Society and Research Centre and printed at  
R. R. Enterprises, 18 - A, Old Gobind Pura Ext., Street No. 2, Parwana Road, Delhi - 110051, Tel: +91 - 8447494107,  
Published from Rajiv Gandhi Cancer Institute and Research Centre, D - 18, Sector - 5, Rohini, Delhi - 110085

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