Non-Muscle Invasive Bladder Cancer

Patient Leaflet

Information for patients diagnosed with non-muscle invasive bladder cancer and undergoing treatment with SYNERGO®

Bladder cancer

Bladder cancer is the 6th most common malignancy among men, and the 17th most frequent among women.
More than 500,000 new cases of bladder cancer are diagnosed worldwide every year. Approximately 75% of these cases are non-muscle invasive disease originating in the bladder wall lining (urothelium). This type of tumour tends to recur, mostly as non-muscle invasive cancer, despite treatment.
A tumour that penetrates more deeply into the muscular layer of the urinary bladder is called "invasive" bladder cancer.

No. of new cases per year	USA & Canada	Europe	UK
	82,000	204,000	10,500

Data sources: World Health Organization (WHO)2020 and Cancer Research UK 2018

Symptoms of the disease

The symptoms of bladder cancer, which are not necessarily clinically evident, generally include:

- Visible presence of blood in urine (haematuria), which is generally painless
- Evidence of blood in urine in laboratory tests
- Urinary urgency (inability to postpone urination) and frequency (urinating often)
- Discomfort during urination

These symptoms may also appear in other non-malignant diseases such as urinary tract infection, urinary bladder stones, benign tumours and others. Only a doctor can interpret the relevance of these symptoms, therefore the appearance of any one of these presentations requires medical attention.

Diagnosing and defining the penetration (stage) and the aggressiveness (grade) of the disease

In order to identify the source of the symptoms, the doctor asks specific questions about the patient's health and performs a physical examination. Later, the doctor may use an instrument that enables direct visualisation inside the bladder, during a procedure called cystoscopy. During this procedure tissue samples of the bladder wall (biopsy) may be collected for examination under the microscope. In case of suspicion of tumour during cystoscopy, a surgical removal known as Transurethral Resection (TUR) will normally follow.
A tissue sample is usually necessary in order to determine the tumour (grade) and the extent to which it has penetrated into the bladder wall (stage). The doctor may need to refer the patient for further evaluation.

Preparing for treatment

Patients often prefer to be actively involved in the clinical decision-making process. A lot of information is available on bladder cancer and the different treatment options. Patients are advised to consult with the medical staff and request all relevant information. Feelings of anxiety and tension are normal in this situation and family support is very important.
It is advisable to prepare a written list of all questions troubling you, before reporting to your doctor, and for a family member to accompany you during the visit.

Treatment of (non-muscle invasive) bladder cancer

The treatment of non-muscle invasive bladder cancer includes two main stages:
a. Surgical removal of tumour by TUR (see above in section on diagnosis). This is performed through the urethra, under regional or general anaesthesia with no need to open the abdominal cavity. In case of numerous tumours, the doctor may need to perform successive TURs or an extensive operation. Occasionally partial or complete (also called radical) removal of the urinary bladder is required (removal of the bladder is called cystectomy), especially when the tumour involves the muscle layer. In this case an alternative route for drainage of urine is then created.

b. Once the type of tumour is ascertained and the risk for recurrence and progression is evaluated, preventive therapy is usually administered by flushing the bladder with either a chemotherapeutic or a biological agent (bladder instillations, also called intravesical therapy). Flushing with chemotherapeutic agents targets cancer cells that were not removed during the operation or that have a high malignant potential. Biological flushing agents, such as BCG (weakened live bovine tuberculosis bacteria) and others, are intended to generate an immune response in the urinary bladder tissue and lead to the destruction of cancer cells.

The doctor will recommend the type of treatment based on the tumour's characteristics and the patient's condition. The decision as to the most appropriate treatment, its consequences and chance of success, will be explained by the doctor and medical team.

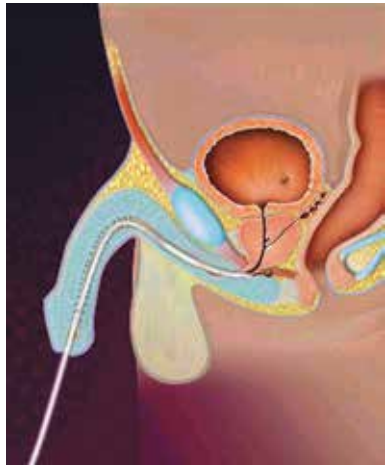
SYNERGO®

The Synergo® Treatment: Local Microwave (RF) Induced Hyperthermia and Chemotherapy

In spite of the variety of treatments available, the rate of tumour recurrence and disease progression have been high among bladder cancer patients at intermediate and high risk of tumour recurrence.
Synergo® device combines local radiofrequency energy, tissue thermal elevation (heating) of the bladder wall, with simultaneous flushing of the urinary bladder with a cooled chemotherapeutic agent (thermochemotherapy).
The RF and chemotherapy are administered locally through a special unique transurethral RF ablation applicator equipped with a miniaturised antenna and five thermometers, all mounted inside a silicone foley catheter.
The applicator is inserted into the urinary bladder through the urethra.
All treatment data is processed and monitored by the Synergo® computer, so bladder tissue temperatures remain constant and stable throughout the treatment (±42 degrees Centigrade).

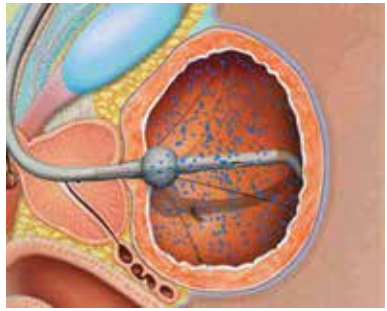
The Synergo® transurethral RF applicator performs three main functions:

1. Radiofrequency radiation (local, non-ionising) of the bladder walls, also uniformly heating them by means of a small RF-emitting antenna.
2. Temperature monitoring by sensitive thermocouples in several locations on the bladder wall and urethra.
3. Circulation of the cooled chemotherapeutic drug into and out of the bladder.



The Synergo® applicator inserted through the urethra

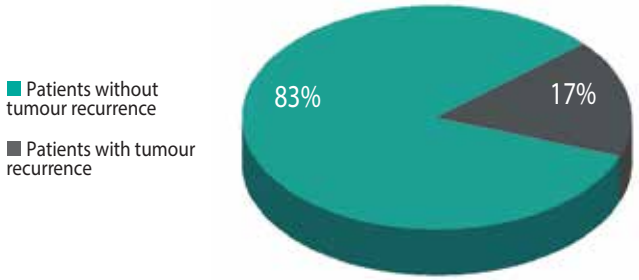
The use of Synergo® was approved by the European Standard Authorities (CE) in 2001. Since then, the treatment has become available in many leading medical centres.



The Synergo® catheter placed in the bladder. Radiofrequency and chemotherapy are uniformly distributed

So far, thousands of patients have been treated with Synergo® worldwide and many studies (including randomised trials) have been conducted over the years.
Synergo® technology has been proven safe and effective in numerous routine treatment studies and clinical trials that have been published since 1995.

There are two indications for treatment with Synergo® (both for intermediate and high-risk of recurrence tumours):
a. Treatment for the prevention of tumour recurrence (prophylactic treatment). For patients who have undergone complete tumour removal by surgery (TURBT) or by laser fulguration (TUF).
b. Treatment for the destruction of tumour (ablation treatment) For patients with extensive tumour or large malignant areas in the bladder, tumours difficult to remove in a single surgical procedure, patients suffering from very frequent recurring tumours, and for patients who are at high operative risk.



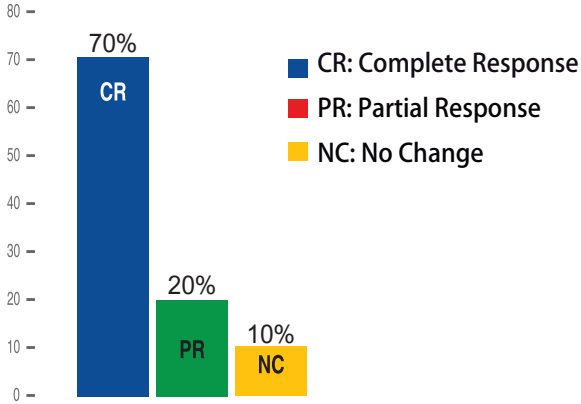
*Result of Synergo® - Prophylactic treatment (2 year follow - up) **

** Colombo R., et al: Comparative study of intravesical chemotherapy alone versus intravesical thermo-chemotherapy for prophylaxis of recurrence of superficial transitional cell carcinoma of the bladder. J Clin Oncol. 21:4270-4276;2003*

In both treatment approaches, the patient is treated with a series of weekly one-hour treatments with no need for anaesthesia. After the weekly sessions, further treatment is given every 6-8 weeks. The treatments are given on an outpatient basis and the patient returns to his/her daily activities immediately thereafter. Side effects from treatments are usually mild and transient (local pain, burning sensation during urination, urgency and frequency of urination), and frequently disappear within 48-72 hours after treatment, without constituting any danger to the patient.

Patient follow-up

Following treatment for bladder cancer, the patient will continue with regular follow-up cystoscopies and tests as required. It is essential that patients comply with the recommended follow-up schedule to ensure that any disease recurrence is identified as early as possible.



* Partial response enabling the removal of the tumor in a single procedure

Result of Synergo® - ablative treatment **

** **Colombo R, et al**: A New Approach Using Local Combined Microwave Hyperthermia and Chemotherapy in Superficial Transitional Bladder Carcinoma Treatment, Journal of Urology Vol 153(3) Mar 1995 **Lüdecke G.,et al**: Radiofrequency hyperthermia chemotherapy (HTC) in high- and extreme high-risk non-muscle-invasive bladder cancer (NMIBC) performed by the German HTC study group: Impressive high chance of organ preservation documented in a cohort study with long-time follow-up Journal of Urology, The Vol. 189, Issue 4, Supplement, p700 2013 **A. Witjes et al.** Intravesical Hyperthermia and Mitomycin-C for Carcinoma In Situ of the Urinary Bladder: Experience of the European Synergo® Working Party World J Urol. 2009 June

The information above is not intended to contain a full and complete description of your condition and should only be viewed as a supplement to the information provided by your doctor. This above is not a substitute for professional medical advice and is to support and not to substitute the discussion between you and your doctor. While clinical studies support the safety and effectiveness of the Synergo System when used in the treatment of non-muscle invasive bladder cancer, results may vary. There are no guarantees of outcome. Before you decide on treatment options, discuss them with your doctor. Understanding the risks of each treatment can help you make the best decision for your individual situation. Synergo treatment may not be appropriate for every individual; it may not be applicable to your condition. Consult with your doctor about all treatment options, as well as their risks and benefits. Only your doctor can determine whether Synergo is appropriate for your situation. The information presented is not a substitute for the good advice of the attending physician.

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