# Introducing a Castrate Resistant Prostate Cancer (CRPC) Model Care Pathway in Belgian Hospitals – towards national standardisation?

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## SUMMARY

Castrate-resistant prostate cancer (CRPC) is characterised by complex strategies for therapy and follow-up. In order to standardise CRPC cancer care on a national basis, an integrated care pathway was devised, based on clinical governance principles and acknowledged best practice, in order to reduce length of hospital stay, reduce costs of patient care, improve patient outcomes (e.g. Quality-of-Life, complications), etc. Therefore, a steering group of Belgian experts, consisting of medical oncologist, urologists, radiation oncologists, oncology nurses, pathologists and nuclear medicines, was assembled to discuss the need for an integrated care pathway for CRPC in Belgium. This was made possible through the financial support of Astellas Belgium. An extensive integrated care pathway was discussed with various stages, depending on the disease status of the patient. Belgian implementation could lead towards further standardisation of cancer care for CRPC patients although several important matters still have to be discussed or adapted. Further assessment and inter-hospital deliberation seems required to ensure a national implementation of the CRPC integrated care pathway.

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## INTRODUCTION

Integrated Care has become a buzzword for seamless patient management since the late 1990s. However, as it is currently applied, the term is often used incorrectly. True integrated care seeks to combine and integrate checklists, standards, evidence and patient data with case management activities and outcome data. Furthermore, the pathway should facilitate regular audit so that a demonstrable improvement in

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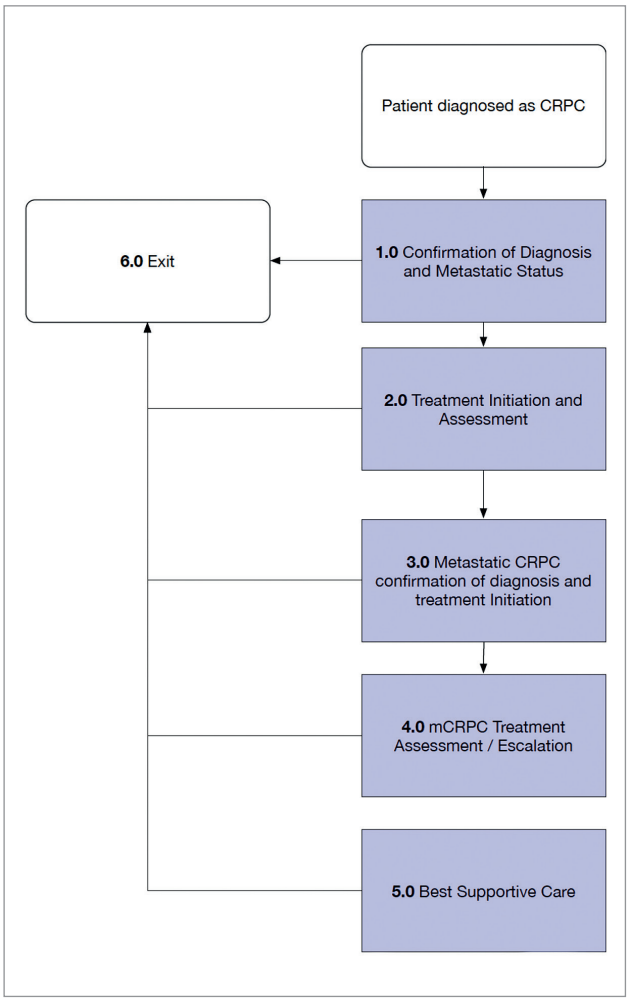


**FIGURE 1:** Integrated Care Pathway for CRPC patients. The model pathway follows the patient journey shown in the diagram. For each part in the patient journey accompanying documents have been worked out in order to facilitate collection of all needed and available data. These documents can easily be adapted or modified according to the needs and choice of the user *(These documents have been added as supplementary information, available online).*

both the process and outcome of care can be achieved. Many integrated care projects fail to achieve these objectives and are in reality nothing more than guidelines or protocols under a different name. In order to deliver true integrated care, clinical governance principles and acknowledged best practice have been applied to this project.[1,2]

The typical Integrated Care Pathway (ICP) comprises a flow chart illustrating the normal patient journey for a defined clinical condition, a document summarising and clarifying the relevant evidence base and a series of forms that provide the day-to-day record and process check for the care of each patient. The opportunities provided by an effectively used and appropriately developed ICP are summarised in *Table 1.*

If applied properly, an ICP can result in several benefits such as a reduction in length of hospital stay, reduction in costs of patient care, improved patient outcomes (e.g. Quality-of-Life, complications), increased patient satisfaction with service, improved communication between staff, increased patient and physician involvement and reduction in time spent on paperwork.

## MODEL CARE PATHWAY FOR CASTRATION RESISTANT PROSTATE CANCER (CRPC) IN BELGIUM

As the advantages of an effective ICP are clearly described, a steering group of Belgian experts was assembled, consisting of medical oncologists, urologists, radiologists, radiation oncologists, oncology nurses, pathologists and nuclear medicines, to discuss the need for an ICP for prostate cancer in Belgium. Believing that it would be impossible to cover the entire ICP for prostate cancer, starting from primo-diagnosis until the end of metastatic treatment, the steering group decided to focus on an ICP for CRPC patients from moment of castration-resistance until end of treatment of metastatic CRPC patients.

The currently established ICP for CRPC patients is depicted in *Figure 1.* This ICP has been designed in 2018 to facilitate the implementation of guidance and best practice in the management of CRPC according to the state-of-the-art and related to the Belgian situation. The ICP is intended to represent a model pathway for Belgian physicians and hospitals that can be amended or modified to suit the capability and capacity of any institution or region. Its main purpose is to facilitate communication across the multidisciplinary team and to ensure that an appropriate care plan is implemented for each patient. During this patient journey, several stages can be traversed from start of the ICP until patients finally exit the ICP. Several documents accompany each stage of the patient journey. *These documents have been added as supplementary information, available online.*

### CONFIRMATION OF DIAGNOSIS AND METASTATIC STATUS

At the moment the patient visits the healthcare specialist, it is imperative that the disease status is correctly identified. In this matter, only patients who have evidence of disease progression during treatment with androgen deprivation therapy (ADT) will be considered to have castration-resistant disease and can enter the ICP. During this first stage, clinicians are required to gather all information needed to determine the actual disease status of the patient and to decide on further treatment options.

At first, general physical examination is required in order to

**TABLE 1.** Opportunities provided by an ICP.[1,2]

- Support multidisciplinary care
- Encourage simple record-keeping
- Allow locally determined standards to be set
- Facilitate clinical audit
- Decrease unwanted variance from the normal pattern in patient care
- Enhance communication between clinical staff, and with patients leading towards improved patient satisfaction
- Provide a structured plan for patient care
- Describe the expected progress for a "typical" patient
- Outline the normal timescale of events
- Present the procedures to be followed, in the right order therefore improving quality standards
- Is backed up by evidence
- Incorporate guidelines based on best practice

assess general and urological symptoms (especially ureteral obstruction and bladder outlet obstruction). In addition, it is also imperative to assess the presence of any neurological symptoms as well as the presence of pain (preferable using the Visual Analog Scale).[3] For completion of the patient history, previous and current therapies should be recorded. Next, disease progression can be identified. This should be done by either laboratory analyses, namely increase in serum prostate-specific antigen (PSA) in the context of testosterone in the castration range, which usually precedes the onset of clinical symptoms by several months, as well as by imaging to prove the occurrence of new metastases and/or progression of existing metastases. Different imaging modalities can be used to describe the presence of metastatic disease, such as CT/PET imaging (thoracic and abdominopelvic for assessment of soft tissue lesions and observation of 'flare' phenomenon), whole body MRI (assessment of bone and soft tissue lesions) and bone scan (progression in case of appearance of at least two new lesions, confirmed at least six weeks later due to possible 'flare' phenomenon).[4-6] Please note that it is highly advised to perform imaging at regular intervals in asymptomatic patients with a stable PSA concentration. This as the PREVAIL trial has indicated that 1 in 4 patients in this patient population does have radiographic progression despite no progression in PSA concentration.[7]

Patients with non-metastatic disease should be categorised as M0 CRPC patients. Although no international accepted criteria exist to define CRPC, the EAU guidelines stipulate the following definition: castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either biochemical progression (defined as three consecutive rises in PSA one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL) or radiological progression (defined as the appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion). Symptomatic progression alone is not sufficient.[8-10]

Next to the determination of the (metastatic) CRPC status, other tests can be performed in order to complete patient records and improve patient care. First, histology assessment can provide new information and may be mandatory for inclusion in clinical trials. Secondly, neuron-specific enolase / chromogranin A can be determined as both are linked with development of CRPC and poor survival in patients diagnosed with CRPC who have normal PSA concentrations. Thirdly, bone mineral density should be considered to assess possible ADT induced osteoporosis. Lastly several other laboratory tests, such as serum creatinine, liver enzymes, haemoglobin, alkaline phosphatase, lactate dehydrogenase and electrolytes, should be conducted in compliance with good clinical practice and to determine possible treatment-related toxicities and prognostic factors.[11-24]

Based on all gathered data, disease status can be determined and treatment can be initiated. Please note that it is essential that all possible treatment options are discussed in a multidisciplinary team meeting (clinicians, oncology nurses, pathologists, etc.) in order to select the most optimal treatment modality for the patient.[25] If applicable, consider if patient can participate in a clinical trial or other potential study/project. Subsequently, the family physician must be informed of the outcome of the multidisciplinary team meeting and he/she should be invited to participate herein.

## TREATMENT INITIATION FOR NON-METASTATIC CRPC AND ASSESSMENT

Firstly, a full clinical evaluation must be performed including ECOG performance status determination and, for elderly patients, G8 assessment. This tool was developed by the International Society of Geriatric Oncology (SIOG) PCa Working Group (PCWG) which recommended that treatment of elderly patients should be based on a systematic evaluation of health status.[17]

At treatment initiation, clinical evaluation was already done during stage 1 of the patient pathway (see *Confirmation of diagnosis and metastatic status*) whereas this can change during the course of the therapy. In this matter, PSA evaluation is of utmost importance for follow-up of patients diagnosed with non-metastatic CRPC. It is the opinion of international experts that second-line hormonal therapies should not be given to chemotherapy-naïve men with non-metastatic CRPC who are at low risk of developing metastases, for whom watchful waiting is considered to be a preferred option.[26] This risk of developing metastases is defined by low PSA concentrations in combination with a long PSA doubling time.[6,27] Again, results of all clinical evaluations should be discussed in a multidisciplinary meeting to determine the most appropriate evidence-based treatment.[25] Several phase III trials have been / are being conducted in search for novel therapies in these patient cohorts. Currently available treatment options, to be administered depending on patient symptoms, consists of corticosteroids (low cost and favourable toxicity profile with no proven survival benefit), denosumab, abiraterone acetate and enzalutamide.[28-33] However, despite positive results in clinical trials, the current guidelines do not (yet) support the use of these cancer-directed treatments in non-metastatic CRPC.[29,34] As the need for novel therapeutics to delay the onset of metastatic disease is high, enrolment of patients with non-metastatic CRPC into clinical trials is recommended.

Once decided, the clinician, assisted by the oncology nurse, can explain all viable treatment options to the patient and come to a treatment decision in accordance with the patient (joint decision making). During this process, it is important to inform the patient what to expect from the administered therapy, which are the possible (and most reported) side effects, which are the possible interactions with other medications and who to contact in case of questions or occurrence of side effects (oncology nurse or prescriber). If desirable, all information can be assembled into a patient information booklet.

During therapy, patients with non-metastatic CRPC will undergo repeated review and follow-up until disease progression. Depending on the status of the patient, the response to therapy (i.e. PSA concentration and PSA doubling time), symptomatic improvement, good psychological coping and good treatment compliance, follow-up should be scheduled every one, two or three months. It is also recommended to perform regular imaging, in patient with M0 CRPC who receive any form of systemic treatment.[34] Interim contacts with the oncology nurse can also be scheduled if desired or needed. Also make sure the family physician is informed following every follow-up visit of the patient.

## METASTATIC CRPC CONFIRMATION OF DIAGNOSIS AND TREATMENT INITIATION

Unfortunately, almost all prostate cancer patients will suffer from metastatic CRPC throughout the course of their disease.[35] As stated for the confirmation of absence of metastases in non-metastatic CRPC, several imaging modalities can be used to confirm the metastatic disease status, as has been described above (see *Confirmation of diagnosis and metastatic status*). Depending on the visceral and/or bone metastatic status, several first-line treatment options have been shown to improve OS, namely docetaxel, abiraterone, enzalutamide and radium-223. Cabazitaxel is an approved second line option after docetaxel. [8,36-49] In addition, several pain management therapies and bone therapies (zoledronic acid, denosumab, calcium / vitamin D) should be considered in order to improve patient' comfort. Imperative when giving bone therapy, is that possible occurrence of bone therapy-induced complications such as osteonecrosis of the jaw are strictly monitored (e.g. via expert stomatologic control).[17,31,50] Lastly, clinical trials should also be considered.

It is important to stress the role of the multidisciplinary team in this phase of the process. Due to the extent of first-line treatment options available for patients with metastatic CRPC, it is greatly recommended to discuss every patient in order to select the optimal treatment regimen per patient.[25] Which therapy is given greatly depends on the physical conditions of the patient. In this matter, ECOG and/or Karnofsky performance status, pain assessment as well as the G8 health status screening tool have to be checked whether or not patients are fit enough to receive systemic therapy for their illness or should receive best supportive care (BSC).

Comparable to patients with non-metastatic CRPC, joint decision making will lead to the optimal and preferred treatment choice for the patient. Depending on the type of treatment initiated, the patient should be thoroughly informed. Next to all above-mentioned essential information that has to be reported to the patients, special attention must be given to the risk of spinal cord compression.[51]

Next, if desired by the patient, psychological support as well as support at home can be provided. If possible, and if ap-

propriate, introduce end of life planning with the patient covering the following basics: vital testament, legal issues, financial issues, religious issues and BSC. The role of the oncology nurse in this stadium of the process is very important as he/she will function as the primary point of contact with the patient and as liaison between patients and the attending physician.

Finally, follow-up / assessment should be planned. Depending on the status of the patient, the response to therapy (i.e. PSA concentration and PSA doubling time), symptomatic improvement, good psychological coping and good treatment compliance, follow-up should be scheduled every one, two or three months. It is also recommended to perform regular imaging (every 6 months at least), in patients who receive any form of systemic treatment.[34] Interim contacts with the oncology nurse can also be scheduled if desired or needed. Also make sure the family physician is informed following every follow-up visit of the patient.

## METASTATIC CRPC TREATMENT ASSESSMENT/ ESCALATION

During follow-up for treatment of metastatic CRPC, a full clinical evaluation must be performed as described previously (see *Confirmation of diagnosis and metastatic status*) with special attention to pain assessment and treatment-related adverse events. Comparable to assessment in patients with non-metastatic CRPC, several biochemical test are mandatory to evaluate the disease status: testosterone / PSA (evaluation biochemical disease progression), serum creatinine (possible bilateral ureteral obstruction or bladder retention), liver enzymes (assessment treatment toxicity), calcium / vitamin D (assessment of possible induced osteoporosis), CRP (adverse prognostic factor in metastatic CRPC) and INR (evaluate blood coagulation in case of disseminated intravascular coagulation or treatment with oral anticoagulants in combination with enzalutamide).[8,17,52] Additionally, presence of new metastases or progression of metastases already present at first-line metastatic treatment initiation can be monitored using CT imaging and bone scan. If required, a MRI scan of the given segment of the axial skeleton can be performed whereas whole body MRI is not recommended.[4-6]

Patient having a clinically good evaluation and who do not progress on their current therapy should be followed-up at regular time intervals (1-3 months). Unfortunately, patients will be faced with disease progression at some time during their first-line therapy. At that point, it has to be decided, by means of multidisciplinary team meeting, if further-line treatment is a viable option for the patient in question based on the patient's disease, physical conditions, ECOG and/or Karnofsky performance status, pain assessment and, if needed the G8 health status screening tool.[25] Patients in whom systematic therapy is not / no longer an option, should receive BSC.

If second-line therapy is initiated, numerous treatment modalities are available, namely and depending on first-line treatment received, docetaxel, abiraterone, enzalutamide, radium-223 and cabazitaxel.[53-60] Comparable to first-line treatment initiation, choice for therapy should be made via joint decision making in which patients are sufficiently informed concerning risk and possible expectations (contact with oncology nurse). In addition, pain management therapies and bone therapies should be considered in order to improve patient comfort and clinical trials should also be considered with great attention to possible bone therapy-induced complications.[17,31,50] If not yet done earlier in the process, introduce psychological support, support at home or end of life planning.

Follow-up and reassessment of patients at regular time interval should be continued as long as patients are treated for their metastatic CRPC. In case of third- or further-line therapies, multidisciplinary meetings are vital to discuss the most optimal treatment modality at that time. Research has proven that enzalutamide shows an objective response rate of 23% in fourth- or fifth-line therapy.[61] Whether a docetaxel re-challenge is useful in further-line remains to be determined.[62] Eventually, all patients will progress in such matter that no therapeutic options remain and BSC should be offered.

## BEST SUPPORTIVE CARE

Along the pathway, patients with metastatic CRPC will no longer benefit from therapy or are no longer fit to receive therapy. At that time, only BSC (palliative care) should be offered to the patients. The World Health Organization defines palliative care as '*an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual*.[63] Therefore in order to offer BSC to our patients, physicians can perform a full clinical evaluation at final follow-up to assess general symptoms, ongoing adverse events, co-morbidities and (treatment-related) complications.

In general, BSC should be considered at home. If desired by the patient, further follow-up can be planned with the attending physician. Depending on the clinical evaluation and the needs of the patient, additional therapy (e.g. analgesics, radiotherapy, etcetera) can be prescribed for symptom management, pain management, and anxiety or depression.[8] Contact with the oncology nurse is further encouraged so patients still have a link with the attending physician and medication

## KEY MESSAGES FOR CLINICAL PRACTICE

1. Castrate-resistant prostate cancer (CRPC) is characterised by complex strategies for therapy and follow-up.
2. Implementation of an integrated care pathway (ICP) for CRPC could lead towards improved patient care and high standardisation throughout Belgian centres.
3. Various stages of the ICP can be used depending on the disease status of the patient.
4. ICP can easily be integrated in the electronic patient files used throughout hospitals.
5. Further assessment and inter-hospital deliberation seems required to ensure a national implementation of the CRPC ICP.

can be adjusted in case of increased pain, anxiety, etcetera.
In terms of patient comfort, following items (if applicable) should be addressed: referral to pain clinic, social support, psychological support, mobility, Quality-of-Life (e.g. increased focus on spiritual need[64]), family support, assistance at home, nutritional needs, complications and end of life planning.

### EXIT

The ICP recognises that on some occasions patients leave the pathway (either permanently or temporarily). This information should be recorded into the patient medical file. Possible reasons for exiting the ICP are: admitted to hospital, transferred care elsewhere, death and lost to follow-up.

## PITFALLS ACCORDING TO THE STEERING GROUP TOWARDS NATIONAL IMPLEMENTATION OF THE CRPC ICP

The steering group reached a consensus that implementation of such an ICP could indeed improve patient care with higher standardisation throughout CRPC patient care. However, several items are in need of review in order to enable full implementation of an ICP in Belgian hospitals:
Need of ICP in hospitals already exhibiting high levels of standards for care? Probably only parts of ICP should be implemented, can be adapted to every centre and can have different accents for every multidisciplinary team.
Practical implementation: will the ICP be able to integrate within electronic patient files already implemented in the hospital? Or will this lead to more (repetitive) administrative work?
What about inconsistencies between types of electronic patient files used throughout Belgian hospitals and, in aspect to data sharing between hospitals, will this be in compliance with current GDPR requirements?
High need for constant review of the ICP as the field of prostate cancer is continuously changing. ICP and accompanying guidelines should be reviewed at least every 12 months.

## CONCLUSIONS

We propose the implementation of an ICP for CRPC in Belgium. This could lead towards improved patient care and high standardisation throughout Belgian centres. It has been agreed within the steering committee that the proposed ICP is acceptable for Belgian implementation and could lead towards further standardisation of cancer care for CRPC patients in Belgium, although several important matters have to be discussed / adapted in order to allow implementation of the ICP. Further assessment and inter-hospital deliberation seems required to ensure a national implementation of the CRPC ICP.

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