5.2. Prostate cancer active surveillance and watchful waiting (QP-5) – Testicular cancer adjuvant therapies (QP-6)

5.2.1. Documentation sheet

Description	Proportion of prostate cancer patients in low risk category receiving no active treatment. Proportion of testicular cancer patients in low risk category receiving no adjuvant treatment after orchiectomy.
Rationale	In Belgium, prostate cancer is the most frequent cancer type in men with 9050 new cases in 2016[q], but few men (3%) die of it. Good clinical practice recommendations advise practitioners to discuss first with a patient diagnosed with localised prostate cancer whether an immediate treatment is required or not. [1] For patients in the low risk category, active surveillance is recommended rather than an intervention for patients. [2] Active surveillance involves close monitoring of biochemical or histological progression with initiation of curative therapy at a given moment. There is currently no clear protocol of active surveillance but periodic exams (as digital rectal exam, PSA measurement and sometimes biopsy) are always foreseen. This approach should be distinguished from watchful waiting (WW) which involves a policy of observation and the provision of (palliative) treatment when symptoms arrive. WW should be recommended to all men with localised disease, irrespective of their risk category, in patient with a short (< 10 years) life expectancy. Testicular cancer is a less frequent cancer (403 new cases in 2016 in Belgium[q]) which generally affects men in the 20-39 age category (over 66% in 2016). [3] Good clinical practice recommendations advise surveillance after surgical testis removal (not to be confused with lymphadenectomy) in case of stage I disease (i.e. localised tumour), especially in absence of risk factors (i.e. rete testis invasion and tumour size in case of seminomas and vascular invasion in case of non-seminomas. [4] Alternatively, active adjuvant treatment (i.e. chemotherapy or radiotherapy or retroperitoneal lymph-node dissection) can be prescribed.
Calculation	Prostate cancer: Numerator: number of patients receiving no active treatment Denominator: number of prostate cancer patients with adenocarcinoma in the low risk category (cT1-cT2 cN0/x cM0/x and Gleason <7) Testicular cancer: Numerator: number of patients receiving adjuvant treatment after surgery Denominator: number of testicular patients with clinical stage I disease treated with orchiectomy
Data source	Belgian Cancer Registry (BCR): incidence years 2004-2015. IMA – AIM
Technical definition	Selection of patients: • new diagnoses of cancer registered in the BCR, with the following ICD-10 code: C61 (for prostate cancer), C62 (for testicular cancer) • for prostate cancer: Adenocarcinoma • for testicular cancer: Clinical Stage I The following exclusion criteria have been applied: • Patients without official residence in Belgium at date of diagnosis

q https://kankerregister.org/Statistiques_tableaux%20annuelle

	• Patients with uncertain incidence date • Patients with no NSSN known • Patients with no IMA data available in incidence year • For prostate cancer: patients with multiple prostate cancers in the period 2004-2015; patients having bladder cancer For analyses on prostate cancer, region corresponds to the region of the place of residence of the patients at time of their diagnosis. Region of the hospital performing surgery is taken into account for analyses on testis cancer. Interventions have been identified for patients thanks to the following billing codes (nomenclature) in the GZSS (health care) IMA – AIM database: • Prostate cancer ○ Surgery: 261796-261800, 694610-694621, 154851-154862, 777114-777125, 172675-172686 ○ Curative external radiotherapy: 444135-444146, 444150-444161, 444172-444183 ○ Brachytherapy: 444216-444220, 444253-444264, 444290-444301, 444312-444323 ○ Chemotherapy has been identified by ATC codes « L01 » with the exception of some CNK codes (710566, 1092857, 1174481, 1174499, 38521 and 706044) in the Pharmanet-Farmanet IMA database. • Testicular cancer ○ Surgery: 261111-261122, 261096-261100, 262570-262581, 241312-241323, 241334-241345, 241872-241883, 241894-241905, 241113-241124, 241150-241161, 260750-260761, 611796-611800, 260713-260724, 260853-260864, 260875-260886, 260890-260901, 262172-262183, 684213-684224, 154932-154943 ○ Curative external radiotherapy: 444135-444146, 444150-444161, 444172-444183, 444113-444124 ○ Retroperitoneal lymph node dissection: 240450-240461, 240472-240483, 243751-243762, 243773-243784, 240494-240505, 240516-240520 ○ Chemotherapy has been identified by ATC codes « L01 » with the exception of some CNK codes (710566, 1092857, 1174481, 1174499, 38521 and 706044) in the Pharmanet-Farmanet IMA database ▪ Carboplatin: L01XA02 ▪ BEP (bleomycin + etoposide + cisplatin): L01DC01, L01CB01, L01XA01
International comparability	N/A
Limitation	This indicator comes from administrative and clinical data, not from patient interview; active participation of the patient and compliance to recommendations cannot be measured. A substantial proportion of the prostate cancer patients in the BCR database has an 'unknown' Gleason score (average ±16%), particularly in the early years of the period of interest, explaining the lower absolute number of selected patients in the earlier years. The BCR database does not have information on risk factors (i.e. rete testis invasion and tumour size in case of seminomas, vascular invasion in case of non-seminomas) readily available for testicular cancer patients. Therefore it is not possible to identify the tumours with presence of risk factors. The calculated indicator on adjuvant treatment serves as a proxy for de ESMO clinical practice guidelines. [4]
Dimension	Quality, Patient centeredness
Related indicators	N/A

5.2.2. Results

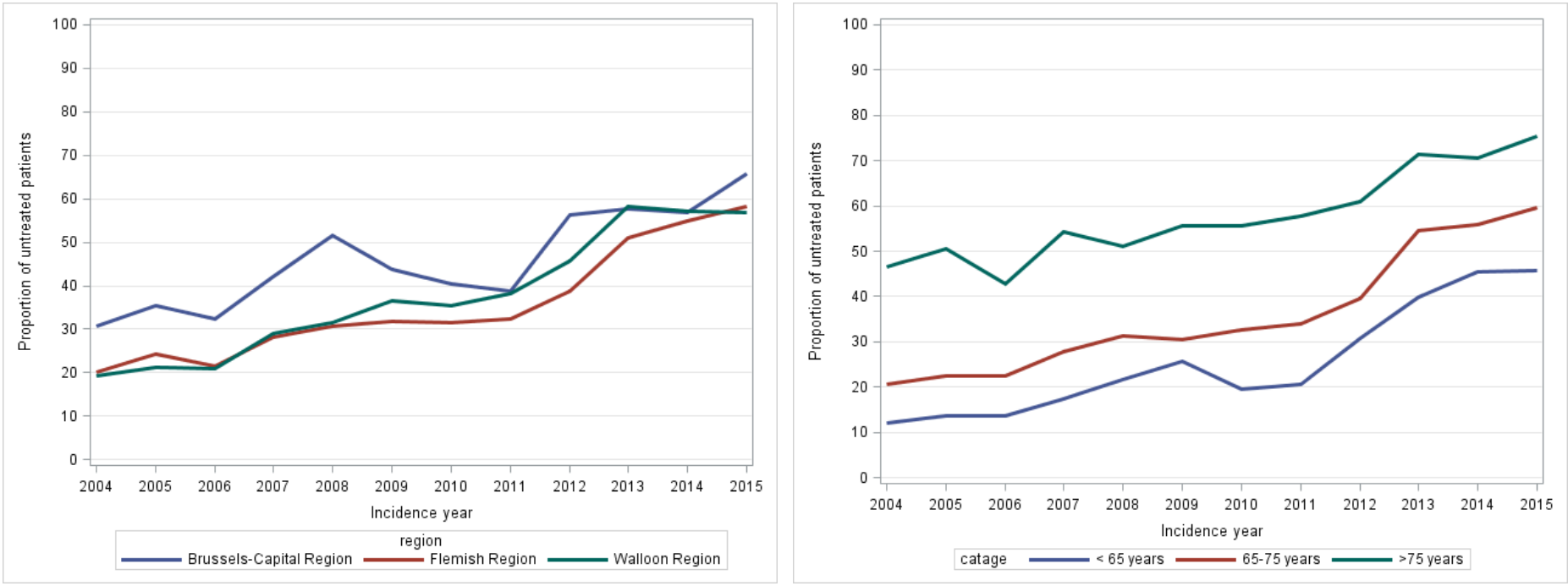
5.2.2.1. Prostate cancer

Low risk category

- "Low risk category" has been defined as a tumour confined to the prostate with no metastasis (i.e. lymph nodes nor distant), and no undifferentiated or poorly differentiated tissue (biopsy):
  - cT1/cT2
  - cN0/unknown
  - cM0/unknown
  - Gleason < 7
- "No active treatment" definition is the following:
  - Patients who receive no surgery, no hormonotherapy, no radiotherapy (RT) (cat. 2-8) within 1 month before and 6 months after the incidence date

There were 37.6% patients with no treatment out of 20 705 for the 2004-2015 period: the older the patients (over 75 years old), the higher the proportion of absence of treatment is, probably indicating a watchful waiting approach (rationale: the patient will probably die from another cause). Moreover for all age categories, the proportion of untreated patients is rising sharply from 2012 on, indicating a general trend towards the recommendation for active surveillance. The effect is most noticeable in men under 65 years old: from 20.7% in 2011 to 45.8% in 2015. Regional variation is generally restricted, and tends to disappear over time (see Figure 61).

Figure 61 – Proportion of prostate cancer untreated patients by age category (left) and by region (right) (2004-2015)



Source: BCR

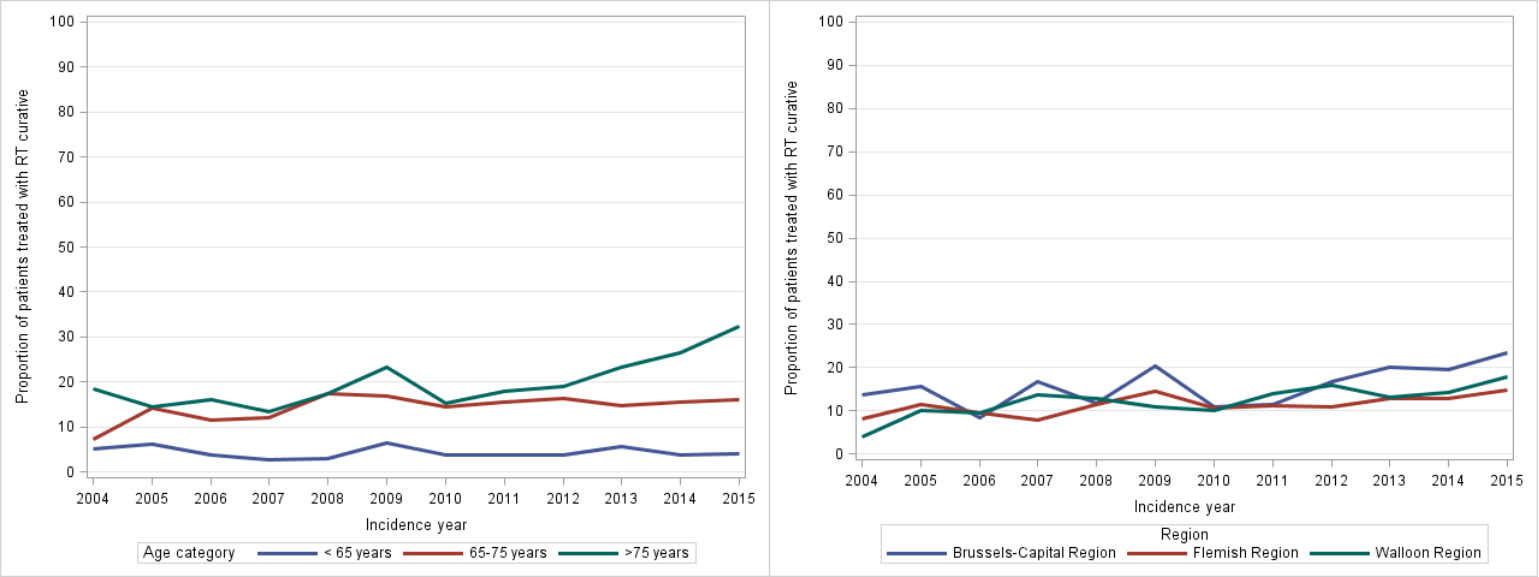
Higher risk categories

As an addendum, some results are presented in this section for prostate cancer patients in higher risk categories.

Patients in the intermediate risk category (cT1-cT2 cN0/x cM0/x and Gleason 7) can be treated by surgery, brachytherapy (localised radiotherapy), external radiotherapy, possibly combined with hormonotherapy. There is no role for chemotherapy in localised disease at this point in time in Belgian (KCE) or international guidelines. The results presented show the proportion of patients getting curative external radiotherapy a primary treatment: these patients didn't receive any surgery nor brachytherapy. Since 2013, the number of patients over 75 years old are getting this less invasive treatment more often compared to their younger counterparts: the rate doubled from 2010 to 2015, to reach over 30 percent of these patients by 2015. There is a discrete generally (all ages) increasing trend of primary curative external radiotherapy observed in all regions, with Brussels a bit ahead Flanders and Wallonia (Figure 62).

The interpretation is quite complex, but it may suggest that older patients are receiving less primary hormonotherapy. The overall incidence of radiotherapy remains quite low suggesting that the treatment decision is primarily driven by urologists.

Figure 62 – Prostate cancer patients in intermediate risk category getting external radiotherapy by age and by region (2004-2015)



Source: BCR

5.2.2.2. Testicular cancer

There were 1516 tumours studied (clinical stage I: localised tumour which can be surgically removed) from 1504 patients over the period 2004-2015. Tumours were classified as seminomas and non-seminomas using the definition of EUROCARE-5 study. As there is no direct link between the cancer (from BCR database) and the treatments found in the IMA data, time frames around the incidence date are used:

- The surgery is considered as related to the cancer if it occurs within 1 month before and 6 months after the incidence date
- A treatment is considered to be adjuvant if it is given within 3 months after surgery[5]

Guidelines have recommended recommend surveillance after surgery for a stage I tumour: KCE guidelines[6] (2010) and ESMO guidelines[4] (2013). The analysis distinguishes two period: before ESMO guidelines 2004-2012 and after (2013-2015). The goal is to reduce long-term side effect of radiotherapy and chemotherapy.

The BCR database does not have information on risk factors (i.e. rete testis invasion and tumour size in case of seminomas, vascular invasion in case of non-seminomas) readily available for testicular cancer patients. Therefore it is not possible to identify the tumours with presence of risk factors. The calculated indicator on adjuvant treatment serves as a proxy for de ESMO clinical practice guideline. In comparison, a recent Spanish publication reported 47% rete testis invasion in stage 1 seminoma [7] and another publication reported 18% vascular invasion. [8]

Seminoma

Most Belgian patients diagnosed with a seminoma stage I (N=913 tumours, 908 patients) receive as primary treatment a surgery (i.e. orchiectomy) (96.9%, N=885 tumours, 880 patients). Since the publication of the ESMO guidelines in 2013, surveillance is recommended following primary orchiectomy, especially in absence of certain histological risk factors (i.e. rete testis invasion and tumour size in case of seminomas) instead of adjuvant treatment (in case of seminoma stage I recommended adjuvant treatment options are 1 cycle of Carboplatin or radiotherapy 10 fractions of 2 Gy). Most stage I patients (79.5%) from the period 2004-2012 received an adjuvant treatment (i.e. chemotherapy or external radiotherapy), compared to only 52.3% for the 2013-2015 period (Table 31). Regional variations are observed, with Wallonia having a bit more than a third of patients (36.5%) with an adjuvant treatment in 2013-2015, compared to more than half of the patients for Flanders (57.2%) and over two thirds in Brussels (69.2%); annual figures are presented in Figure 63 (remark: Brussels has no more than 10 cases a year, explaining the wide variations). When looking at the proportion of stage I patients receiving adjuvant external radiotherapy (with or without chemotherapy), there has been a remarkable decrease between the 2004-2012 period (30.6%) and the 2013-2015 period (3.6%); this has been observed in Flanders (drop to 2.6%) and Wallonia (drop to 4.1%) and in a milder way in Brussels (drop to 15.4%). The same has not been observed when considering chemotherapy as adjuvant therapy (with or without radiotherapy): the proportion remained stable at 49% (2004-2012 vs 2013-2015 periods).

Table 31 – Proportion of stage I testicular cancer (seminoma) with adjuvant therapy (chemotherapy or radiotherapy) following surgery

	Belgium			Brussels			Flanders			Wallonia		
Before ESMO guidelines (2004-2012)	604	480	79.5	52	46	88.5	380	309	81.3	171	124	72.5
After ESMO guidelines (2013-2015)	281	147	52.3	13	9	69.2	194	111	57.2	74	27	36.5

Figure 63 – Proportion of testicular cancer patients (stage I, seminoma) with adjuvant treatment (chemotherapy or radiotherapy) following surgery by region (2004-2015)

Source: BCR

Most patients (69.9%) from the period 2004-2012 had an adjuvant treatment (carboplatin-based chemotherapy or radiotherapy) whereas only 44.5% had it for the 2013-2015 period (Table 32). Regional variations are observed, with Wallonia having less than a quarter of patients (21.6%) with the mentioned adjuvant treatment in 2013-2015, compared to half of the patients for Flanders (52.6%) and Brussels (53.9%); annual figures are presented in Figure 64 (Brussels has no more than 10 cases a year, explaining the variations).

Table 32 – Proportion of stage I testicular cancer (seminoma) with adjuvant therapy (carboplatin or radiotherapy) following surgery

	Belgium			Brussels			Flanders			Wallonia		
	N surgeries	N adjuvants	%	N surgeries	N adjuvants	%	N surgeries	N adjuvants	%	N surgeries	N adjuvants	%
Before ESMO guidelines (2004-2012)	604	422	69.9	52	41	78.9	380	279	73.4	171	101	59.1
After ESMO guidelines (2013-2015)	281	125	44.5	13	7	53.9	194	102	52.6	74	16	21.6

Source: BCR

Interpretation: In absence of information on the risk factors incidence, we can conclude that a significant proportion of patient is still receiving adjuvant treatment.

Figure 64 – Proportion of testicular cancer patients (stage I, seminoma) with adjuvant treatment (carboplatin-based chemotherapy or radiotherapy) by region (2004-2015)

Source: BCR

Non-seminoma

There were 572 tumours (569 patients) with non-seminoma stage I testicular cancer included in the study over the period 2004-2015. Non-seminoma is defined according to EUROCARE-5 study (ICD-O morphology codes = 9080-9083; 9085; 9100-9102; 9065; 9070-9072); 97.2% (556 cases) were treated with surgery (i.e. orchiectomy) as primary treatment.

The difference in adjuvant treatment between the period 2004-2012 and 2013-2015 is smaller than for seminoma (Table 33): a mean proportion of 66.8% of the operated patients received an adjuvant therapy in 2004-2012 compared to 59.9% in 2013-2015 for Belgium. There is a regional variation, with the highest rates of adjuvant treatment in Flanders, followed by Brussels, and the lowest rates in Wallonia. The generally observed decrease of adjuvant treatment over time is of similar order of magnitude in the 3 regions.

Table 33 – Proportion of stage I testicular cancer (non-seminoma) with adjuvant therapy (chemotherapy or retroperitoneal lymph node dissection) following surgery

	Belgium			Brussels			Flanders			Wallonia		
Before ESMO guidelines (2004-2012)	404	270	66.8	37	22	59.5	278	202	72.7	89	46	51.7
After ESMO guidelines (2013-2015)	152	91	59.9	9	5	55.6	102	67	65.7	41	19	46.3

Source: BCR

Key points

- **Practitioners are advised to actively involve the patient in the choice of treatment; for patients diagnosed with a tumour in early stage, the patients can be involved in the decision-making whether to treat immediately or to postpone or to leave out the treatment (e.g. active surveillance, watchful waiting)**
- **The proportion of prostate cancer patients with an early stage low risk tumour (cT1-cT2 cN0/x cM0/x and Gleason <7) getting an active treatment around the diagnosis date is declining in the more recent years (i.e. 2012-2015): 58% of the patients diagnosed in 2015 received no treatment (all ages) compared to 21% in 2004; regional variation for these results is very small; throughout the whole study period (2004-2015) the proportion of patients without treatment around the diagnosis date is clearly higher in patients aged 75 years or older compared to younger patients**
- **The proportion of prostate cancer patients aged 75 years or older in an intermediate risk category (cT1-cT2 cN0/x cM0/x and Gleason 7) getting a less invasive treatment (external radiotherapy) rather than surgery or brachytherapy as primary treatment is rising since 2011 and is over 30% in 2015**
- **Testicular cancer patients (stage I, localised cancer) have a primary surgical treatment (i.e. orchiectomy) which can be followed within 3 months by an adjuvant treatment or surveillance; since 2013, ESMO guidelines recommend surveillance after orchiectomy for stage I seminomas and non-seminomas rather than adjuvant treatment, especially in absence of risk factors; a clear decrease in proportion of adjuvant treatments has been observed for the 2013-2015 period compared to the period preceding the publication of new guidelines in case of seminoma (especially for adjuvant radiotherapy), and to a much less pronounced extent in case of non-seminoma; these trends are observed in all regions**
- **Regional variation regarding adjuvant treatment for stage I testicular seminoma shows the highest rates for Brussels, followed by Flanders and lastly Wallonia, both before and after the publication of new guidelines**
- **Regional variation regarding adjuvant treatment for stage I testicular non-seminoma shows the highest rates for Flanders, followed by Brussels and lastly Wallonia, both before and after the publication of new guidelines**

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