Is ISUP-1cancer?

By Erik Briers, Europa Uomo Vice Chairman

At the end of November 2024, I was invited to Vienna for a debate during the PROSCA international meeting entitled: “Should we still call ISUP-1 (Gleason 3+3) prostate cancer, cancer?” Three experts participated in the debate, exploring whether it would be helpful or not to re-categorise these low grade tumour growths, which are unlikely to cause death: urologist Roderick van den Bergh, pathologist Eva Compérat and myself as a patient representative. The participants were mainly urologists, along with radiation oncologists and some pathologists. At the start of the debate, those in the room were allowed to express their view in a vote. The result was that 82% were in favour of still calling ISUP grade group 1 growths “cancer”. The debate was moderated by Oxana Komina and Bertrand Tombal.

The arguments for a change: Roderick van den Bergh

Roderick van den Bergh opened the debate and argued the position that we should no longer call growths in ISUP grade group 1 “cancer” (it should be noted that although he held this position for the sake of debate, it is not necessarily his own). Dr van den Bergh said that the debate had been ongoing for years, in publications dating back to 1982 – a time when the PSA test had not yet been introduced.

Those advocating for a different name for ISUP-1 “cancers” cite a study reported in European Urology Focus in 2023 (doi: 10.1016/j.euf.2023.04.002) which investigated the opinions of 1,303 urologists, radiation oncologists, and pathologists related to low grade prostate cancers. It found that 83% routinely recommended active surveillance and never regretted it, while just 2% routinely recommended active surveillance and often regretted it. When asked whether opposed to giving these growths a “non-cancer” name, 61% of pathologists opposed it compared to 25% of urologists. Overall, 39% of respondents thought that a new name was a good idea, 31% disagreed, and 30% were undecided (see figure 1). The preferred new name was “neoplasm with low malignant potential”.

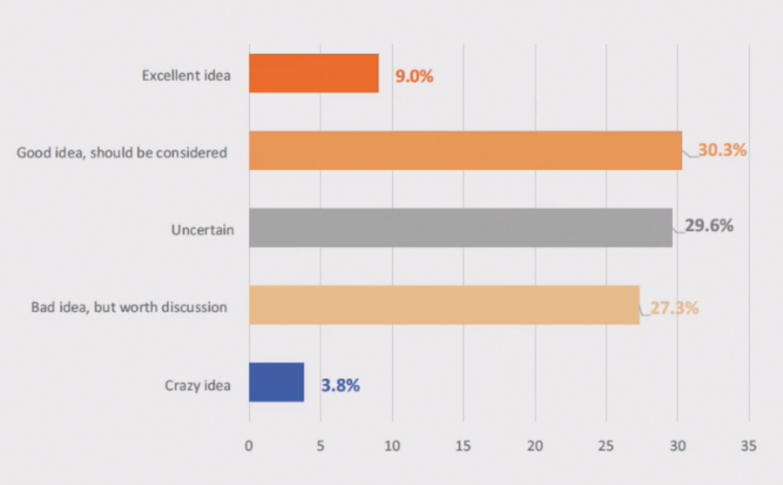

Figure 1

Supporters of a change argue that ISUP grade group 1 has long been considered as not a cancer. Published studies have found that ISUP grade group 1 is rarely found outside the prostate, and metastases to the lymph nodes are also rarely found. Urologists would prefer not to find it because they would then have to do something about it such as initiating active follow-up. If it were not called cancer, this would be unnecessary and ISUP-1 growths would be considered part of men's ageing process.

The pathologist's view: Eva Compérat

At the PROSCA meeting, pathologist Eva Compérat was clear: yes, ISUP-1 is cancer.

Pathologists examine biopsies and other tissues removed by surgeons, including lymph nodes and metastases.

According to pathologists, ISUP-1 shows all the characteristics of cancer under the microscope. There are patients who die from prostate cancer after being diagnosed with an ISUP-1 cancer, and in such cases higher-grade cancers (Gleason 7-10) are always found. This may be because a higher grade was originally missed or because the low grade cancer evolved to a Gleason grade 7 and further, eventually leading to metastasis. So for the pathologist, ISUP grade group 1 (Gleason 3+3) remains an adenocarcinoma, cancer.

Pathologists decide, based on microscopic examination, whether what they see should be considered cancer and what is "benign" and "malignant". The difference centres on whether the cancer can metastasise, migrate to other parts of the body and grow there. With prostate cancer, we know that this cancer can nest in bone but also in the lungs and other organs.

A "benign" tumour remains at the site where it originated. But from my own point of view, I would say that this does not mean a benign tumour is harmless: quite the contrary. A glioblastoma, for example, remains at the site where it originated but it is

deadly. By occupying space in the brain, important functions are disabled and the life expectancy for this “benign” cancer is around 12-18 months.

The patient perspective: Erik Briers

I was invited to speak on behalf of the patients. Could I represent the opinion of all patients? I cannot say, but over 20 years I have kept my finger on the pulse, continually listened to patients, and learned a lot as a member of the European Association of Urology committee that establishes the guidelines for the treatment of prostate cancer. The arguments I used came from those many opinions.

In short, for patients, ISUP-1 prostate cancer is cancer. We endorse the scientific argument presented by Professor Compérat that ISUP-1 exhibits all characteristics, both morphological and molecular, of cancer, so it is cancer.

ISUP-1 and cancer risk.

There are other factors, part from ISUP classification, that can be used to classify cancers into risk groups. According to the D’Amico risk stratification system used by the European Association of Urology to classify prostate cancer patients, the risk groups can be categorised as follows:

Low risk: PSA < 10ng/mL AND ISUP-1 (Gleason Grade 6 (3+3)) AND cT1-2a, based on a rectal exam, a non-palpable tumour, or limited to less than half of one half of the prostate or less.

Intermediary risk: PSA 10-20 ng/mL OR ISUP-2 or ISUP-3 (GG 3+4 of 4+3) OR T2b, tumour in more than half of one half but not in both halves. Low-intermediary risk would then be ISUP-2 (3+4) and high-intermediary risk ISUP-3 (4+3).

High risk: PSA > 20ng/mL OR ISUP>3 (4 or 5) OR cT2c, the tumour is found in both halves of the prostate in a rectal exam.

Each of these “classes” says something on the potential evolution of the cancer. The risk of progression is higher in high-risk than in low-risk.

In low-risk prostate cancer, three indicators must be simultaneously fulfilled: the tumour identified by the pathologist must be an ISUP-1 and no higher; the PSA must be lower than 10ng/mL; and the cancer must be limited to no more than half of one half upon a rectal exam.

For an average risk, the PSA is between 10 and 20ng/mL, or an ISUP-2 or ISUP-3 is found by the pathologist. But this means that a PSA of 15 with an ISUP-1 is also average risk. A PSA above 20ng/mL with an ISUP-1 is high-risk cancer and requires active treatment.

Let us think about the consequences of “declassifying” ISUP-1 cancer

Suppose we start calling ISUP-1 not cancer but something else. Then we have a problem with men who have an average or high risk due to a higher PSA value. With a PSA of less than 10, we send these men home because there is nothing – but maybe months or years later, the man returns and we find a PSA above 20ng/mL. Then it is suddenly high-risk cancer. We cannot call the same ISUP-1 “not cancer” simply when it suits us.

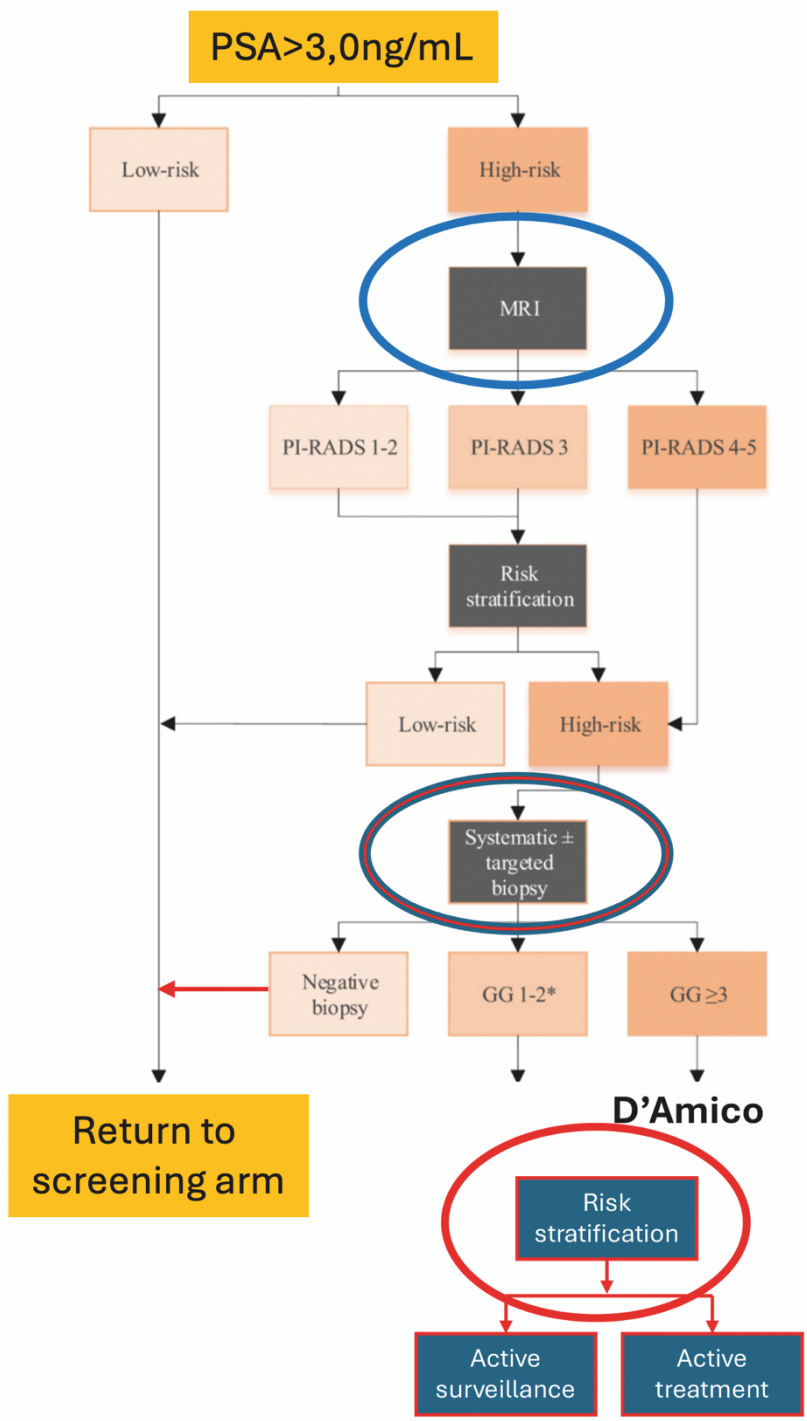

Figure 2

ISUP-1 in the screening algorithm

And what about screening? Screening presents another argument against a name change. Figure 2 shows part of the screening algorithm proposed by the European Association of Urologists. If a man has a PSA of 3ng/mL or higher, an evaluation is conducted. If this raised value can be explained by, for example, prostate enlargement, the process stops and the man returns to the screening arm. If there is no explanation for this PSA value, the man is referred for an MRI. If the MRI indicates risks (PI-RADS 4-5, sometimes 3), biopsies are taken and analysed by the pathologist. The biopsy result can be negative, after which the man returns to the screening arm, or a tumour with a Gleason grade 6-10 which is further evaluated to formulate a treatment proposal.

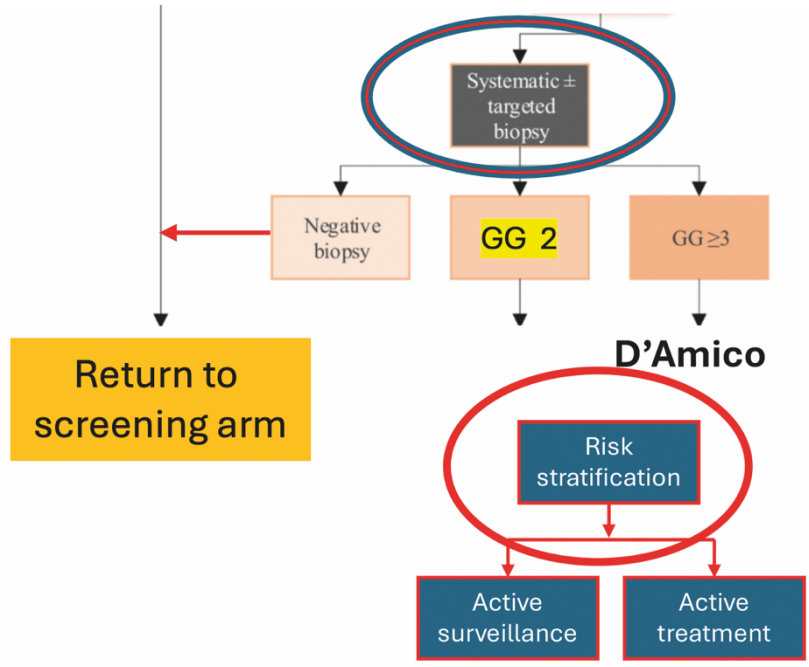

Figure 3

Figure 3 shows part of the algorithm if we no longer consider an ISUP-1 as cancer. In that case, all ISUP-1cancers are reported as "negative" biopsies. During the evaluation, the ISUP-2 (GG 2) can receive the proposal of active surveillance by the clinician. But the large group of ISUP-1 cancers no longer exists. This should not be underestimated, because it concerns up to 50% of the cancers diagnosed today. They are all sent back to the screening arm.

However, these men all showed risk factors on their MRI – possibly PI-RADS 4-5 or a doubtful PI-RADS 3. Moreover, they have undergone unpleasant biopsies. Next year, they are likely to receive a new invitation for a PSA test which could again be 3ng/mL or higher – and this may lead to biopsies again. There is a risk that this group of men

will ignore further screening due to previous experiences, knowing that nothing was amiss. For many, this will be correct. But not for all, as for 12-24% of the ISUP-1 cancers, there can be an increase in risk. These cases must be found, because if not properly monitored or treated they can become metastatic cancers.

Suddenly, prostate cancer becomes less benign, more deadly.

ISUP-1 in cancer statistics

In Belgium, the Cancer Registry collects information about all cancer diagnoses along with several data points that are important for monitoring. The stage at which cancer is diagnosed ranges from 1 to 4, with stage 1 being cancers that are only moderately malignant (but real cancers nonetheless) and stage 4 being cancers that are truly malignant and have already spread. For prostate cancer, there were 12,699 new cases in 2022 (see figure 4). Data was missing for two of these, and the data was incomplete for 577 making classification impossible: these are collected under "X."

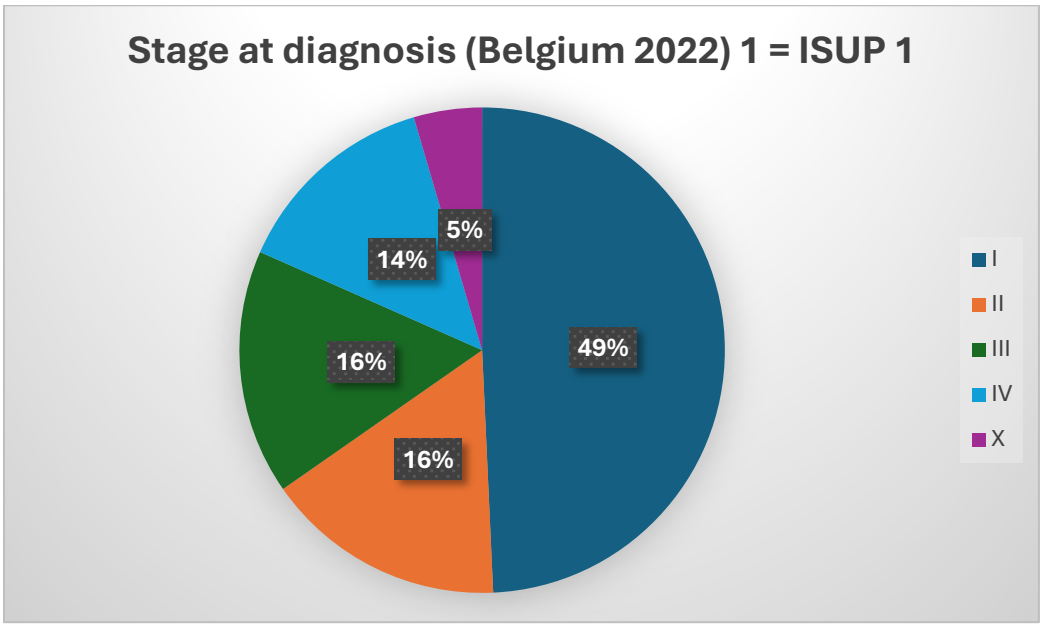

Figure 4

Of the 12,699 new cancers, 6,256 fall under stage I, which – as an approximation – we can describe as ISUP-1 (Gleason 3+3). This means that almost 50% of all new prostate cancers in 2022 should have been treated with active surveillance (whether this actually happened, we do not know).

Supposing we classify ISUP-1 as “not cancer” and label the biopsies as negative. Then there remain 6,443 new diagnoses, including the two incomplete cases and the 577 that fall under "X." The classification changes completely (see figure 5).

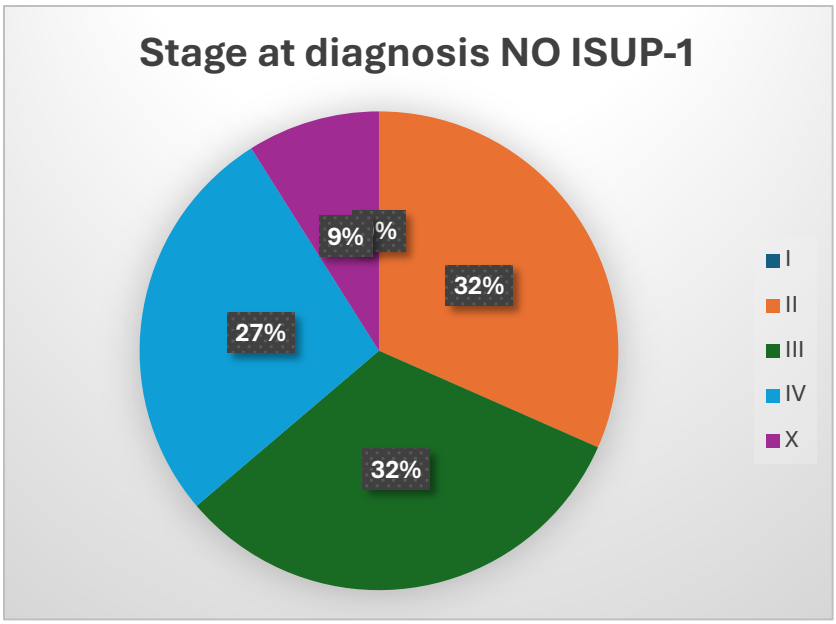

Figure 5

We then have three almost equal groups, with stage IV becoming very important at 27% – meaning that more than a quarter of the new diagnoses are already metastatic.

What does this mean comparing prostate cancer to other significant cancers? Figure 6 shows Belgian Cancer Registry statistics for the ten most important cancers affecting men in 2022.

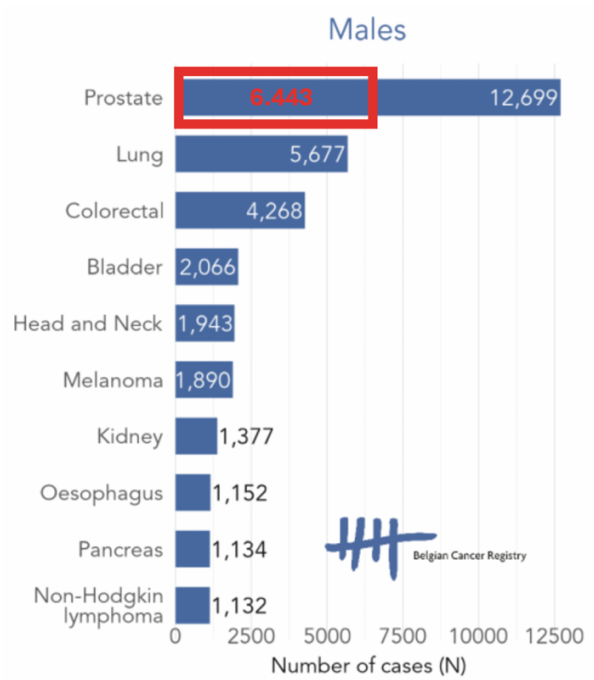

Figure 6

The blue bars show the statistics as we know them, including even the ISUP-1 cancers in prostate cancer. In 2022, we see 12,669 cases of prostate cancer, making it without doubt the most important cancer in men. The red frame on the top bar shows what happens if we no longer call ISUP-1 cancer. This leaves 6,443 cases, with prostate cancer still the most important cancer for men.

This change makes no difference to prostate cancer mortality, which remains the same. in 2020 nearly 1,600 men died from prostate cancer – comparable to the number of diagnoses made where the cancer had already metastasised.

If we look at the total number of all cancers, there were 41,774 new diagnoses in 2022. If we filter out the low-grade prostate cancers, 35,518 cases remain – a (fictitious) reduction of 15%.

But we must not forget that ISUP-1 is indeed cancer and not a benign condition. The consequences of reclassifying ISUP-1 as "not cancer" would be significant globally. All countries worldwide would have to participate in the redefinition.

Protecting the patients?

Some doctors want to give low-grade cancers a different name because they believe it would be better for patients. They think that men have to be protected from the psychological issues that come with the word “cancer”.

They argue that we do not want to find these low-grade cancers – only high-grade malignant cancers should be found and treated. They find it difficult to explain to men that they have a low-grade cancer that does not require immediate treatment – that these low-grade cancers need to be actively monitored or, if the man has less than ten years to live due to other illness, simply forgotten (watchful waiting).

We understand that it can be very difficult for doctors to explain these things to patients in just 8-10 minutes – the time of a consultation. We appreciate it can be quite frightening for patients to be told they have cancer and then be told: "But we don't need to do anything about it now; we will monitor you very well."

In the face of this, it can be tempting for doctors to quickly give in to patient concerns and suggest active treatment for low-risk prostate cancer. In such cases, they do not always reveal the full truth about expected side effects.

Europa Uomo research involving more than 6,000 men in Europe, the USA, Canada, and Australia posed patients questions about the side effects they experienced after their cancer treatment. We can easily isolate the group of local and locally advanced prostate cancers from this large study. It clearly shows one thing: regardless of whether the treatment was surgery or radiation, up to half experienced sexual

dysfunction. With surgery, up to one in five experienced incontinence. On the other side, there are no such side effects with active surveillance.

In other words, however low-grade prostate cancer is named, it should be actively surveilled, with the scalpel remaining sheathed and the robot in the barn.

Conclusion

For patients, low-grade prostate cancer remains cancer. There is no need for a new name. However, we men must be brave enough to accept that there is such a thing as active surveillance, where these cancers are picked up and only treated curatively if they become dangerous after months or years. Until then, enjoy life!

Based on the article
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