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A RANDOMIZED CONTROLLED INTERVENTION TRIAL ON LIFE STYLE AND INTERACTION WITH MICROBIOTA IN PROSTATE CANCER PATIENTS UNDERGOING RADIOTHERAPY (MICROSTYLE)

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Summary

1 ABSTRACT

Background: Prostate cancer (PCa) is the second most common cancer in men worldwide. The standard non-surgical approach for localized PCa is radiotherapy (RT), but one of the limitations of high-dose RT is the potential increase in gastrointestinal and genitourinary toxicities.

Recent findings points to an improvement in toxicity profile and fatigue by healthy lifestyle approaches. Thus, we designed a clinical trial for PCa patients undergoing RT to investigate whether changes towards a healthy lifestyle is able to modify microbiome, improve quality of life and decrease the side effects of RT

Methods: Study participants will be recruited among men undergoing RT in two Italian centers (Milan and Naples). We foresee to randomize 300 patients in two intervention arms: Intervention Group (IG) and Control Group (CG). Participants allocated to the IG will meet a dietitian and a physiotherapist before RT to receive personalized diet and exercise recommendations, according to their health status, to improve overall lifestyle and reduce side effects (bowel and/or urinary problems). All participants (IG) will be given a pedometer device (steps counter) in order to monitor and to spur participants to increase physical activity and reduce sedentary behavior. Participants included in the CG will receive baseline general advice and materials available for patients undergoing RT. According to the cross-over design, the CG will cross to the intervention approach after 6 months, to actively enhance compliance towards suggested lifestyle recommendations for all patients.

Preliminary results: To date, we have enrolled 19 patients (10 allocated to IG and 9 to CG) in the two centers. Median age was 70 (range 55 - 80) years. They referred to be former smokers 58%, smokers 26%, and 16% never smokers. Median body weight was 81 kg (range 60 – 112 kg), body mass index was 28 (range 20 – 38 kg/m^2) and Waist to Hip Ratio was 1.0 (0.9 – 1.3).

Discussion: This trial is innovative in its design because we propose a lifestyle intervention during RT, which includes both dietary and physical activity counselling, as well as monitoring changes in microbiome and serum biomarkers. The promotion of healthy behavior will be initiated before initiation of standard care, to achieve long lasting effects, control side effects, cope with feelings of anxiety and depression and improve efficacy of RT.

Abbreviations

PCa: Prostate cancer; RT: radiotherapy; IG: Intervention Group; CG: Control Group; RC: randomized controlled trial; IMRT: Intensity-Modulated RT; QoL: Quality of life; ECOG PS: Eastern Cooperative Oncology Group Performance Status Scale; BMI: body mass index; MUST: Malnutrition Universal Screening Tool; hs-CRP: High-sensitivity C-reactive protein; IL-6: Interleukin-6; LH Luteinizing hormone; RTOG: Radiation Therapy Oncology Group; EORTC: European Organization for Research and Treatment of Cancer; WCRF: World Cancer Research Fund

2 PROSTATE CANCER

2.1 The cancer processes

The predominant theory, formulated in the middle of the last century, indicate cancer as a set of about 200 diseases from abnormal cell growth, released from the normal control mechanisms of the organism. The process of transformation of a normal cell into a neoplastic cell occurs through various stages with accumulation of genetic, functional and morphological anomalies. The proliferation (cell division) is a physiological process that takes place in almost all tissues and in countless circumstances: normally there is a balance between proliferation and programmed cell death (apoptosis) (Gruppo di lavoro AIOM, AIRTUM, Fondazione AIOM, PASSI, PASSI D'Argento, 2019).

According to the last report of the World Cancer Research Fund(WCRF/ AICR, 2018), each time a cell in the body divides into new daughter cells, there is potential for a mutations in the DNA sequence. These errors may result in non-functioning genes or in the production of proteins with altered amino acid sequences, which can modify the cells function. These mutations can lead to an uncontrolled cell division and tumor formation. Moreover, DNA can be also exposed to external environmental factors such as ultraviolet (UV) light and cigarette smoke or internal reactive oxygen species (ROS), hydroxyl radicals and hydrogen peroxide, which can damage DNA, affecting its structure and integrity. The DNA is also exposed to dietary factors (food and micro and macronutrients), physical activity and excess body fatness that can modify hormones and the immune system. All of them can modify or protect the DNA integrity.

Cancer develops when the processes that control the normal cell behavior fail and a cell becomes the progenitor of a group of cells characterized by functional abnormalities. Almost all solid tumors can be characterized by a relatively small number of functional abnormalities. These characteristics (not related to genetic factors) have been classified by WCRF (WCRF, 2018) the 'hallmarks of cancer' as reported in **Figure 1**. These are ten characteristics all involved with disordered control of cell function and two of them are fundamental enabling characteristics: genomic instability and mutation AND tumor-promoting inflammation.

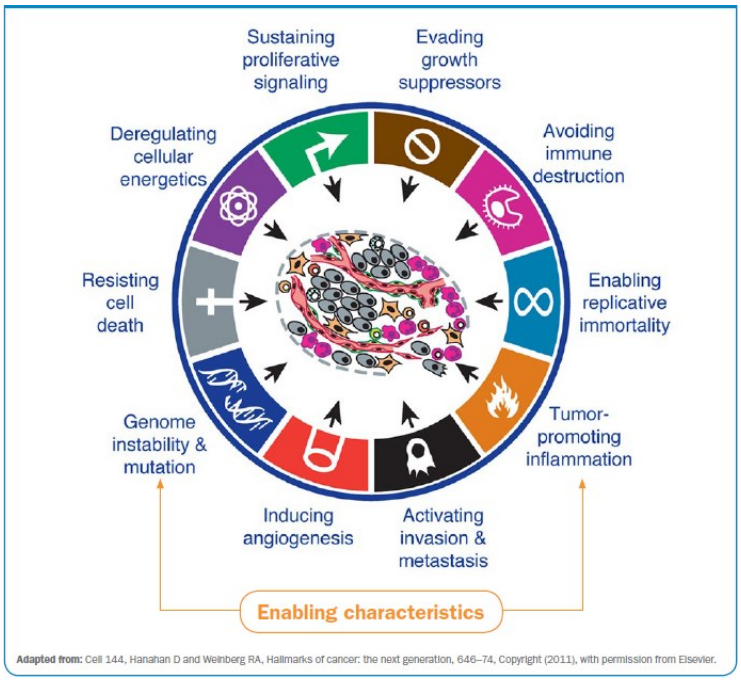

Figure 1. The ten hallmarks of cancer cells (WCRF/AICR 2018)

The cancer event requires more than one mutation in different classes of genes. The loss of proliferation control occurs as a result of mutations in genes which control cell repair processes DNA, cell division and cell death. Our organism is able to repair and to activate the immune system, to combat the transformation processes but, when these processes fails, the cell is transformed into a cancer cell. Therefore are necessary the activation of the oncogene (genes that promote growth) and the tumor suppressors that inactivate the genes that inhibit growth (**Figure 2a and 2b**).

Carcinogenesis it is a long and complex process and in most cases they take several years. It could in fact lie dormant for many years until a light bulb turns on. One single genetic alteration rarely is sufficient for tumor expansion. Normally a carcinogen works on cellular DNA and causes a process of initiation, followed by the promotion of neoplastic growth. Other factors must interfere to facilitate the progression of the disease and some mechanisms are essential for growth tumor. Microenvironment that is present around the tumor is important to favoring cells, growth factors, but also cells that damage or kill cancer cells.

More than one mutation is generally necessary to lead to cancer and sometimes one of the mutations is inherited. People that present such inherited mutations are identified at high risk of developing cancers. Although such familial cancers are uncommon, inherited genetic mutations can cause about 5% to 10% of all cancers (https://www.cancer.gov/about-cancer/causes-prevention/genetics). Most cancers, however, result from the accumulation of genetic damage in cells over time and are not related to a single inherited mutation.

Another important mechanism needed for the progression of the cancer is the angiogenic switch. The tumor is able to grow undisturbed when it is able to build its own blood vessels.

Figure 2a

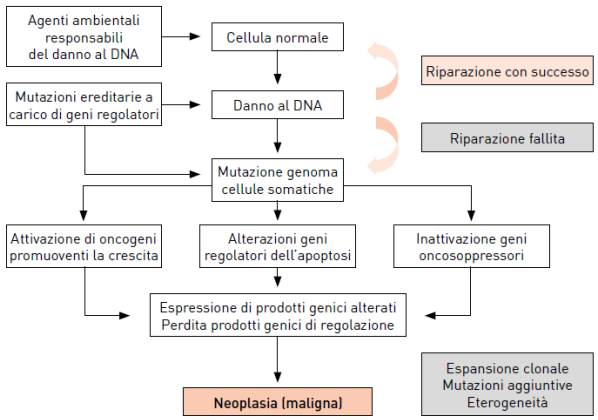

Figure 2b

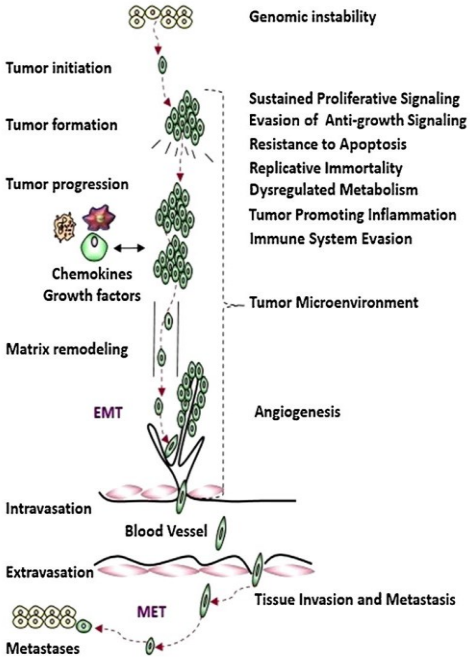

Figure 2a. The pathways of carcinogenesis (Gruppo di lavoro AIOM, AIRTUM, Fondazione AIOM, PASSI, PASSI D'Argento, 2019)

Figure 2b: Stages of cancer development and the hallmarks of cancer (WCRF/ AICR, 2018)

Established causes of cancer

The cancer process is the result of a complex interaction involving environmental and lifestyle factors with host factors that are related both to inheritance or through epigenetic change. Host factors are important and they can influence susceptibility to cancer development, in particular related to aging. This cause both opportunities to accumulate genetic damage, as well as impairment of function, such as DNA repair processes. The interaction between the host metabolic state, food consumption, nutritional status, sedentary lifestyle, level of physical activity and other environmental exposures over the whole life course, can affect protection and/or susceptibility to cancer development. Invasive cancer can progress to a significant disease taking many years.

The factors that compromise the normal regulation of cellular processes and ultimately lead to cancer are categorized into three main groups as reported in **Figure 3**:

- **Endogenous factors** arising from processes within the body, such as sex, hormonal, immune system, microbiome**,** metabolic factors or inherited genetic mutations;
- **Exogenous factors** derived from the environment**,** such as food contaminants, environmental carcinogens, virus, UV radiation;
- **Diet/lifestyle factors** linked to the dietary pattern, nutrient and bioactive compounds, alcohol consumption, sedentary lifestyle and/or physical activity level.

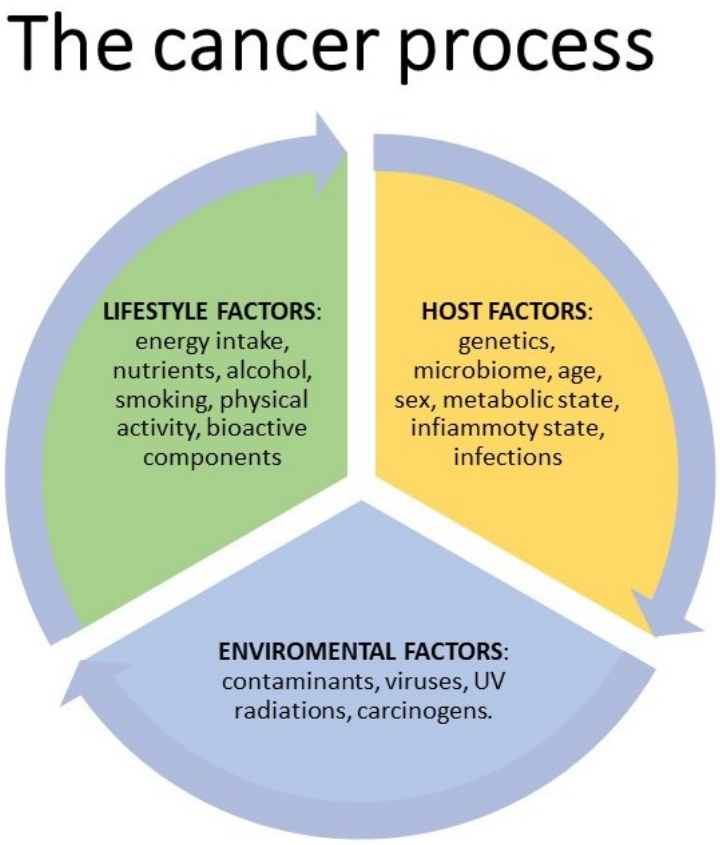

Figure 3: Lifestyle, environmental exposures and host factors interact to affect the cancer process (WCRF/ AICR, 2018)

The fraction of cancer attributable to lifestyle and environmental factors are reported in **table 1**. According to data published by American Association for Cancer Research (Landen & Lengyel, 2013) in the USA, tobacco smoking alone was responsible for 33% of cancers; another 33% is linked to lifestyles factors such as diet, overweight, alcohol and physical inactivity.

Occupational factors are responsible for 5% of cancers. Infections cause about 8% of tumors (Papilloma virus for uterine cervix, Epstein-Barr for lymphoproliferative and oral lesions, Herpes-virus for Kaposi's sarcoma and lymphomas, Helicobacter pylori for stomach carcinoma and lymphoma MALT, hepatitis B and C virus for hepatocellular carcinoma) and parasitic infections from Trematoid for cholangiocarcinoma and those from Schistosoma for bladder carcinoma. Ionizing radiation and exposure to UVA rays are responsible for 2% of cancer and environmental pollution contributes another 2%.

In the United Kingdom, data published by Parkin et al. (Parkin et al., 2011) reported that the four most important lifestyle exposures were tobacco smoking (19.4%), dietary factors (9.2%), alcohol drinking (4%) and bodyweight (5.5%), accounting for 38% of the cancers occurring in 2010 – almost four-fifths of the total from all 14 exposures. Population-attributable fractions provide a

valuable quantitative appraisal of the impact of different factors in cancer causation, and are thus helpful in prioritizing cancer control strategies.

Risk factors	**Fraction of cancer attributable to various risk factors**	
	US, 2021	UK, 2010
Smoking	33%	19.4%
Dietary factors	5%	9.2%
Overweigh, obesity	20%	5.5%
Physical inactivity	5%	1.0%
Alcoholic beverages	3%	4.0%
Occupational factors	5%	3.7%
Infections	8%	3.1%
Ionizing radiation and UV exposure	2%	5.3%
Environmental pollution	2%	-

Table 1. Fraction of cancer attributable to various risk factors [(Gruppo di lavoro AIOM, AIRTUM, Fondazione AIOM, PASSI, PASSI D'Argento, 2019) modified]

More recently, to estimate the number of deaths from non-communicable chronic diseases (NCD) attributable to behavioral risk factors (RFs) (tobacco smoking, unhealthy nutrition, physical inactivity, overweight, and excessive alcohol use), Carreras estimated the Italian attributable fractions (Carreras et al., 2019) obtained using the Global Burden of Disease Study and applied to the mortality data. About 191,000 out of 614,307 deaths occurred in Italy in 2016 were attributable to combined RFs (about 37% in males; 26% in women). The total amount of deaths attributable to smoking In Italy were 17% and 6% respectively in men and women, 6% and 3% to alcohol abuse; 7% and 8% to overweight; 13% and 12% to dietary RFs, and 2% and 3% to low physical activity. The higher proportion of attributable deaths by age group was recorded in people aged 40-59 years (43% in men; 28% in women).

2.2 Prostate cancer

Prostate cancer is caused by cells in the prostate gland that develop uncontrollably. The prostate is only found in men and is located in front of the rectum, below the bladder, where it generates seminal fluid, which is a component of semen. It is around the size of a walnut under normal circumstances, but it can grow to be considerably larger in elderly males. It can enlarge and cause

problems, particularly in the urinary system. Hormones that influence its growth, such as testosterone, have a high sensitivity to this gland.

Adenocarcinomas account for nearly all prostate cancers. Other types of cancer which can start in the prostate include: small cell carcinomas, neuroendocrine tumors, transitional cell carcinomas and sarcomas.

Prostate cancers can grow and spread quickly in some cases, although most do not. In reality, postmortem examinations have revealed that many older men (and even some younger men) who died of various causes also had prostate cancer that they had never experienced during their lifetimes. In many situations, neither they nor their doctors were aware that they were suffering from it.

Benign diseases that affect the prostate, especially beyond the age of 50, are far more common than carcinomas, and can occasionally present symptoms that are similar to those of a tumor. The core region of the prostate enlarges in benign prostatic hyperplasia, and the overgrowth of this tissue compresses the urethra, the tube that transports pee from the bladder to the outside via the prostate. Urine passage is hampered as a result of the compression.

2.3 Prostate cancer statistics

According to last report published by Global Cancer Statistics 2020 (Sung et al., 2021), PCa is the second most frequent cancer and the fifth leading cause of cancer death among men with an estimated almost 1.4 million new cases and 375,000 deaths worldwide in 2020.

Transitioned countries (countries with a high or very high Human Development Index - HDI) have 3-fold greater incidence rates than transitioning countries (emerging and lower HDI countries/economies) (37.5 and 11.3 per 100,000, respectively), although mortality rates are less varied (8.1 and 5.9 per 100,000, respectively).

PCa is the most often diagnosed malignancy in men in more than half of the world's countries (112 of 185). Incidence rates vary from 6.3 to 83.4 per 100,000 men across regions. The highest rates are found in Northern and Western Europe, the Caribbean, Australia/New Zealand, Northern America, and Southern Africa, while the lowest rates are found in Asia and Northern Africa.

The Caribbean, Sub-Saharan Africa, and Micronesia/Polynesia have the highest death rates. In 48 countries, including many in Sub-Saharan Africa, the Caribbean, Central and South America (i.e., Ecuador, Chile, and Venezuela), and Sweden, PCa is the top cause of cancer death.

The most significant factor to the diversity in PCa incidence rates around the world is likely variability in PCa diagnostic procedures (Zhou et al., 2016). In several countries, such as the United States, Canada, and Australia, the introduction of prostate-specific antigen (PSA) testing enabled for the discovery of preclinical malignancies, resulting in rapid rises in incidence rates in the late 1980s and early 1990s (Center et al., 2012). Within a few years, the large rises were followed by abrupt decreases, indicating a depletion of prevalent hidden malignancies in the general population. Following that, there was a decrease in PSA testing, owing to revisions in the guidelines for PSA-based screening of asymptomatic males, as well as a decline in the incidence rates in the late 2000s (Kvåle et al., 2007).

In China and Eastern Europe (Belarus, Bulgaria, Slovakia), as well as Sub-Saharan Africa, incidence rates have continued to rise between 1995 and 2018. The reasons for the uniform increase are unknown, but they are assumed to be mostly due to increasing awareness and advances in the health-care system, which have enabled a wider use of PSA testing and probably more transurethral resections (Culp et al., 2020; Seraphin et al., 2021). Since the mid-1990s, PCa mortality rates have fallen in most high-income nations, due to advances in therapy and earlier identification through enhanced screening.

In high-resource countries, a more recent trend (2009-2013) indicates that mortality declines are stabilizing (i.e., the United States, Denmark, Norway, Switzerland, Spain, Argentina, New Zealand, Israel, and Japan), but lowering rates persist in some countries (i.e., the United Kingdom, Greece, Italy, Austria, France, Germany, the Netherlands, Brazil, Canada, and Australia) (Bray & Piñeros, 2016; Center et al., 2012; Wong et al., 2016).

Since around 2010, there has been an increase in regional and advanced-stage cancer diagnoses in the United States, as well as a corresponding increase in advanced-stage death rates from 2012 to 2017 (Etzioni et al., 2008). Informed/shared decision-making (i.e., an individual choice of men with their health care provider after receiving information about the uncertainties, risks, and potential benefits associated with the screening) for PSA testing in men at average risk, beginning at age 50 years, has recently been postponed for men aged 55 to 69 years, according to the current American Cancer Society guideline (Grossman et al., 2018; Wolf et al., 2010). In the future, the impact of this change on cancer rates will be determined (Sung et al., 2021).

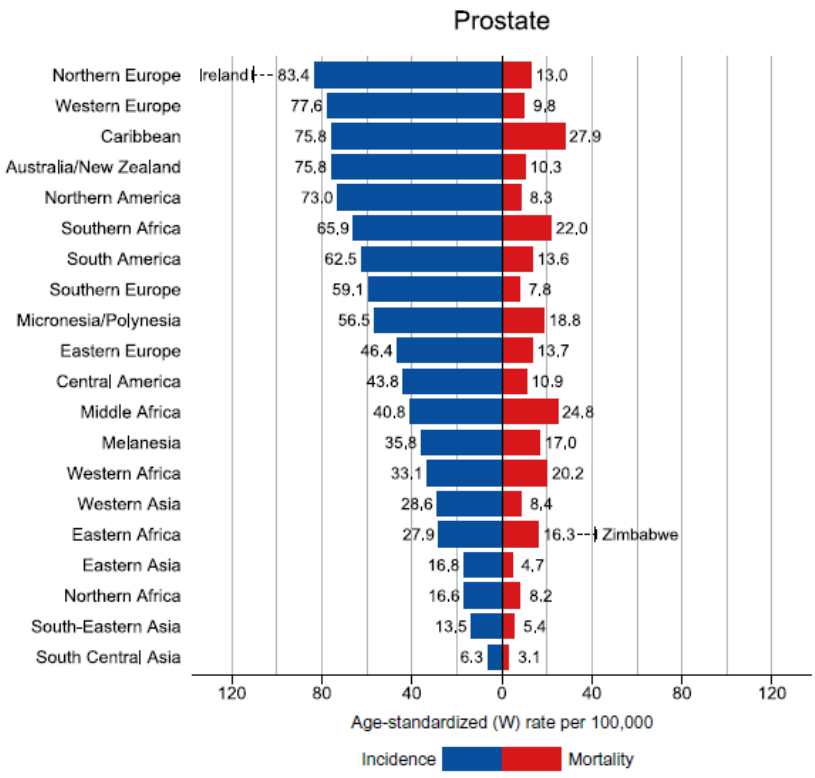

Figure 4. Region-Specific Incidence and Mortality Age-Standardized Rates for Prostate Cancer in 2020. Rates are shown in descending order of the world (W) age-standardized incidence rate, and

the highest national age-standardized rates for incidence and mortality are superimposed (Sung et al., 2021)

In Italy, PCa is the most common cancer in the male population and accounts for 18.5% of all cancers diagnosed in men: estimates for the year 2020 peak of 36,074 new cases a year nationwide. Despite the high incidence, the risk of the disease having a fatal outcome is low, especially if action is taken in time and, compared to 2015, a reduction in mortality rates of (-15.6%) was estimated in 2020 (AIRTUM/AIOM, 2020).

This is also demonstrated by the data relating to the number of people still alive five years after diagnosis - on average 92% - a percentage among the highest in the case of cancer, especially if we consider the advanced average age of patients.

The incidence, which is the number of new cases registered in a given period of time, has grown in the last decade in conjunction with the greater diffusion of tests which, although not always conclusive, have nevertheless helped early diagnosis such as the PSA test (prostate specific antigen) (AIRTUM/AIOM, 2020).

2.4 Risk factors

Age, ethnicity, genetic factors, and potentially dietary factors are the most important known prostate cancer risk factors. PCa is primarily caused by advanced age. Clinically diagnosed PCa is uncommon before the age of 40, but it becomes more common beyond the age of 50, with roughly two out of every three malignancies detected in adults over 65.

The rate of malignancy in males without clinical evidence of PCa based on histologic evaluation of the prostate is substantially higher than the rate of clinically diagnosed disease (Delongchamps et al., 2006). Although the prevalence rates for undetected PCa varied significantly between investigations, they all showed that the prevalence rose greatly with age (Delongchamps et al., 2006).

Some ethnic groups are more likely to get PCa. Black males have lower testosterone levels than White or Hispanic men, which could be due to a combination of dietary and/or hereditary factors (Hankey et al., 1999; Platz et al., 2000).

Prior to the prostate-specific antigen (PSA) era, the annualized average incidence rates for men in their early 70s per 100,000 population were approximately 1600, 1000, and 700 for African Americans, whites, and Asian Americans, respectively, although PSA testing cannot explain the higher incidence of disease in this group of men. Currently, the relationship between ethnicity and race and PCa is a complex mechanism, with discrepancies in access to care, variances in healthcare systems based on geographic location, competing causes of death, systematic racism, and socioeconomic factors all playing a role (Dess et al., 2019).

There is a major genetic component to PCa. Up to 20% of males diagnosed with PCa in the world have a paternal or fraternal family history of the disease (Hemminki, 2012). PCa on either side of the family, especially in a first-degree relative diagnosed before the age of 65, increases the chance of PCa in men by about double (Bruner et al., 2003).

The presence of mutations in some genes can also increase the risk of PCa.

Men with a genetic HOXB13 mutation have a higher risk of developing PCa over their lifespan (Nyberg et al., 2020) and the Lynch syndrome–associated MSH2 gene has a higher lifetime risk of developing PCa (Dominguez-Valentin et al., 2020). In addition, approximately 200 single nucleotide polymorphisms have been related to an increased risk of PCa (Plym et al., 2021).

Although evidence is emerging for smoking, excess body weight, and some nutritional factors that may raise the risk of advanced PCa, there results are not completely convincing.

The link between tobacco use and the development of PCa is still up for debate. While it has been suggested that smoking cigarettes increases the risk of PCa, a meta-analysis found that current cigarette smoking was inversely related with incidence PCa in recent years (Islami et al., 2014). They reported a link between cigarette smoking and aggressive disease, and that smoking more cigarettes per day was linked to a 30% increased risk of dying from PCa. A more recent study found that smoking cigarettes was linked to adverse pathological characteristics of cancer and a poor oncological management (Brookman-May et al., 2019).

Regular exercise appears to lower the risk of disease progression, cancer-specific death, and overall mortality (Campi et al., 2019). Occupational physical activity, on the other hand, has not been linked to a lower risk of PCa in cohort studies (Krstev & Knutsson, 2019) and other researchers have failed to find a significant link between occupational or leisure physical activity and PCa (Benke et al., 2018).

Although several dietary components have been hypothesized to be linked to the risk of overall and aggressive PCa, according to the most recent study issued by the WCRF/AICR (WCRF/ AICR, 2018) only few have been found to be convincing linked to PCa. The results of 104 trials involving almost nine million (9,855,000) participants for a total of 191,000 PCa cases were evaluated in the latest report.

There is strong evidence that being overweight or obese and adult attained height increases the risk of PCa. Furthermore, researchers discovered that beta-carotene consumption (either through food or supplements) has little effect on the risk of PCa. Compared to the previous report published in 2007, consumption of food rich in selenium, selenium supplements and food rich in lycopene have been downgraded from strong evidence of a decreased risk, but no conclusion were presented. The study revealed no link between PCa and dairy products, as well as calcium and vitamin E-rich diets.

Results from the San Antonio Biomarker of Risk prospective study (SABOR) found that saturated fatty acids, trans fatty acids, monounsaturated fatty acids, and cholesterol intake were linked to an elevated risk of PCa in a cohort of more than 1900 men (Liss et al., 2019).

Daily consumption of well-done meat was linked to an increased risk of PCa, in the PLCO screening trial. Cross et al. suggested that heating meats at high temperatures may result in the formation of mutagenic chemicals, such as Heterocyclic amines that heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs). These compounds are known to be carcinogenic that can occur when meat is cooked at high temperatures (Cross et al., 2005). However, a recent meta-analysis of cohort studies found no effect between meat consumption and PCa incidence (Han et al., 2019).

A recent meta-analysis of 27 studies found a link between sugar-sweetened beverages and the risk of PCa (Llaha et al., 2021), but no link between alcohol consumption and the risk of PCa were found. Zhao reviewed 340 studies and found a significantly increased risk of PCa among low (RR =

1.08, P 0.001), medium (RR = 1.07, P 0.01), high (RR = 1.14, P 0.001), and higher (RR = 1.18, P 0.001) consumptions of alcoholic beverages compared to abstainers (Zhao et al., 2016).

Recent reports have found contrasting results. Hong et collaborators reported that total alcohol consumption was not associated with aggressive or non-aggressive PCa (Hong et al., 2020), and on the contrary Vartolomei et al. reported that moderate wine drinking had no effect on the risk of PCa. Surprisingly, moderate white wine consumption increased the risk of PCa by 26%, whereas moderate red wine consumption had a preventive effect, lowering the risk by 12% (Vartolomei et al., 2018).

According to a recent meta-analysis of 16 studies involving over 1,081,000 males, increasing coffee consumption was associated with a 9% decreased risk of developing PCa. In the dose–response analysis, they found a nearly 1% reduction in the incidence of PCa for each additional cup of coffee consumed each day (X. Chen et al., 2021).

Lopez et collaborators recently published a systematic reviews and meta-analyses that found a weak dose-response relationship with total dairy products, milk and cheese, indicating that higher dairy consumption may raise PCa risk, although the evidence on overall is not consistent (López-Plaza et al., 2019).

Zhang and colleagues analyzed the link between phytoestrogen and the risk of PCa. They found that high consumption of phytoestrogen and soy reduce the risk of PCa (Applegate et al., 2018; M. Zhang et al., 2016), while in the PLCO study, however, the results were in the opposite direction. They found that consuming isoflavones increased the probability of advanced PCa (Reger et al., 2018).

Two recent meta-analyses reported by Cheng and Morze that analyzed dietary patterns failed to find a link between adherence to the Mediterranean diet and PCa incidence and mortality (Cheng et al., 2019; Morze et al., 2021).

Although there is some evidence that some nutritional components may play a role in the prevention and progression of PCa, more high-quality studies are needed to comprehend the complicated nature link between dietary consumption and PCa. The available studies are mainly based on self-reported data and may be influenced by variability and errors, as well as the possible effect of measured and unmeasured confounders on the association.

2.5 Symptoms

In its early stages, PCa is commonly asymptomatic. Clinical behavior of PCa can range from asymptomatic, microscopic, well-differentiated tumor that may never become clinically significant to a more rare clinically symptomatic aggressive, high-grade cancer that causes metastases, morbidity and death.

At the time of diagnosis, 77% of PCa cases are confined; 13% have spread to regional lymph nodes, and 6% have distant metastasis (National Cancer Institute. Bethesda, 2021). As the tumor mass expands, urinary symptoms tend to rise and they include difficulty urinating (particularly starting) or needing to urinate frequently, pain when urinating, blood in the urine or semen and a sense of not being able to urinate completely.

Bone pain may be the presenting symptom in the 6% of individuals with metastatic PCa at the time of diagnosis. The most common sign of bone metastases is pain, which is the most prevalent site of disseminated PCa (Collin et al., 2009).

2.6 Diagnosis

An urological examination, which commonly includes rectal examination and PSA testing, is used to diagnose PCa.

PSA levels are frequently elevated in males with PCa. PSA is a protein that is produced only by prostate cells and is highly specific to the prostate gland. Higher PSA value is associated with a higher risk of PCa. PSA is not specific for cancer, and it can increased in a variety of benign illnesses; additionally, a PSA test in the normal range does not rule out the possibility of PCa. PSA is the most widely used and important test for early identification of PCa, despite its lack of specificity for PCa (A W Partin, S R Criley, E N Subong, H Zincke, P C Walsh, 1996; Rabah et al., 2019) (**Table 2).**

Age	Normal reference ranges
40 to 49 years	0 to 2.5 ng/mL
50 to 59 years	0 to 3.5 ng/mL
60 to 69 years	0 to 4.5 ng/mL
70 to 79 years	0 to 6.5 ng/mL

Table 2. PSA normal reference ranges according to age.

A digital rectal examination (DRE) is a type of physical examination that can detect prostate nodules, induration and asymmetry, all of which can be signs of PCa. On the other hand, it is frequently undetectable by DRE because it can only detect tumors in the posterior and lateral sides of the prostate gland, which are the parts of the prostate that are palpable through the rectum.

The 25% to 35% of tumors that are not accessible because they occur in other areas of the gland and the little, and stage T1 malignancies that are not palpable are among those not detected by DRE. In the absence of symptoms, DRE is generally not suggested as a routine screening test for the prostate or rectal area (urinary or rectal). However, if a DRE anomaly suggestive of PCa is discovered, additional investigations are required.

Lower urinary tract symptoms (LUTS) such as frequency, urgency, nocturia, and hesitancy are frequent in men. Rather than PCa, these symptoms are frequently caused by a benign etiology such as benign prostatic hyperplasia (BPH). Patients may be concerned that these or other symptoms caused by anatomic, infectious or irritant etiologies could indicate PCa. Bladder outlet obstruction (BOO), urinary tract infection (UTI), prostatitis, interstitial cystitis (IC), or chronic pelvic pain syndrome can all cause these symptoms (CPPS).

The prostate biopsy is the only test that can confirm the presence of cancer cells in the prostate tissue. Multiparametric magnetic resonance imaging has become essential in determining whether and how to subject the patient to such a biopsy, which is done under local anesthetic in an outpatient or day hospital setting and takes only a few minutes (Moore et al., 2013; Siddiqui et al., 2013).

About 12 samples are usually obtained trans-rectally or trans-perineally (the region between the rectum and scrotum) using the guide of the ultrasonic probe implanted in the rectum, which are then analyzed by the pathologist under a microscope in search of any cancer cells. Prostate biopsy can also be performed in a targeted manner under the guidance of previously performed multiparameter magnetic resonance imaging.

2.7 Staging

When a biopsy confirms prostatic adenocarcinoma, it is graded according to the degree, which indicates how aggressive the illness is, and the stage, which reveals how far it has spread. Physicians can use diagnostic imaging procedures like CT (computed tomography) or magnetic resonance imaging to better define the spread of the PCa. Instead, a bone scan can be used to screen for the presence of any skeleton metastases.

Gleason grading system. The Gleason grade is determined by the architectural characteristics of PCa cells and is highly correlated with clinical outcomes. Tumors are rated from 1 to 5 based on their development pattern and degree of differentiation, with grade 1 being the most differentiated and grade 5 being the least differentiated (Epstein, 2010). A higher score suggests a higher risk of non-organ-confined disease, as well as a worse prognosis after localized disease treatment (Bostwick, 1994; Gleason et al., 1974).

Gleason score. The Gleason score is calculated by adding the numerical values of the two most common differentiation patterns together (a primary grade and a secondary grade). For instance, if a biopsy consisted primarily of grade 3 disease and afterwards grade 4 disease, the cumulative score is "3+4" or 7. As pathologists has gained more experience with Gleason grading, they are less likely to diagnose PCa on needle biopsy with composite Gleason scores of 2 to 5. As a result, the range of composite Gleason scores on prostate biopsies for clinical practice is Gleason 6 to 10.

The Gleason score has long been the standard for grading tumors, and it was included as a critical prognostic feature in the TNM staging approach for PCa in 2010. The Gleason score has been incorporated into the new histologic grade group, which is utilized in allocating patients to prognosis stage groups, in the eighth edition of the TNM staging system (Amin et al., 2017) **(Table 3 and 4**). The TNM system is commonly used, with T indicating tumor size, N indicating lymph node status (N: 0 if not affected, 1 if affected), and M indicating the occurrence of metastases (M: 0 if absent, 1 if present).

The correlation of these parameters (TMN, Gleason, PSA) allows the disease to be classified into three risk classes: low, intermediate, and high. In the case of a low risk (e.g., a disease that is unlikely to spread and cause metastases), it may be decided to forego the surgical removal of the gland and instead focus on monitoring the pathology's inevitable progression.

Prostate cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
Clinical T (cT)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy found in one or both sides, but not palpable
T2	Tumor is palpable and confined within prostate
T2a	Tumor involves one-half of one side or less
T2b	Tumor involves more than one-half of one side but not both sides
T2c	Tumor involves both sides
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
T3a	Extraprostatic extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Pathological T (pT)	
T category	**T criteria**
T2	Organ confined
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
NOTE: There is no pathological T1 classification. *NOTE:* Positive surgical margin should be indicated by an R1 descriptor, indicating residual microscopic disease.	
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional nodes were not assessed
N0	No positive regional nodes
N1	Metastases in regional node(s)
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease
NOTE: When more than one site of metastasis is present, the most advanced category is used. M1c is most advanced.	
Prostate-specific antigen (PSA)	
PSA values are used to assign this category.	
PSA values	
<10	
≥10 <20	
<20	
≥20	
Any value	

Histologic grade group (G)		
Recently, the Gleason system has been compressed into so-called Grade Groups.		
Grade Group	**Gleason score**	**Gleason pattern**
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, or 5+3
5	9 or 10	4+5, 5+4, or 5+5

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Table 3: Prostate cancer TNM staging (AJCC UICC 8th edition) (Klein, 2021)

Prostate cancer TNM prognostic stage groups AJCC UICC 8th edition

When T is...	And N is...	And M is...	And PSA is...	And Grade Group is...	Then the stage group is...
cT1a-c, cT2a	N0	M0	<10	1	I
pT2	N0	M0	<10	1	I
cT1a-c, cT2a, pT2	N0	M0	≥10 <20	1	IIA
cT2b-c	N0	M0	<20	1	IIA
T1-2	N0	M0	<20	2	IIB
T1-2	N0	M0	<20	3	IIC
T1-2	N0	M0	<20	4	IIC
T1-2	N0	M0	≥20	1-4	IIIA
T3-4	N0	M0	Any	1-4	IIIB
Any T	N0	M0	Any	5	IIIC
Any T	N1	M0	Any	Any	IVA
Any T	Any N	M1	Any	Any	IVB

NOTE: When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available.

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; PSA: prostate-specific antigen.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. Corrected at 4th printing, 2018.

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Table 4: Prostate cancer TNM prognostic stage groups AJCC UICC 8th edition (Klein, 2021)

The grade group system. In 2014, the consensus conference of the International Society of Urological Pathology (ISUP) endorsed a new five-tier grading system based on modified Gleason scores (**Table 5**) (Epstein et al., 2016). The 2016 World Health Organization categorization of genitourinary cancers adopts this new grading (ISUP grade group) methodology (Brooks et al., 2015).

The new grade group system is based on the Gleason score and provides more accurate risk classification than the composite Gleason score and it is not designed to replace the Gleason grading system (Epstein et al., 2016).

Based on the primary and secondary Gleason pattern, tumors are divided into five categories (**Table 5**). An examination of nearly 20,000 patients receiving radical prostatectomy at five academic centers between 2005 and 2014 confirmed the grade group approach (Berney et al., 2016; Ham et al., 2017). In the validation study, the risk of PCa mortality increased as the overall grade group increased (Berney et al., 2016).

In the Grade group 2 (Gleason score 3+4 = 7) the hazard ratio [HR] for death was 2.8 compared to grade group 1. In the Grade group 3 (Gleason score 4+3 = 7) the HR was 6.0, in Grade group 4 (Gleason score = 8 (including 4+4 = 8, 3+5 = 8, or 5+3 = 8) the HR was 7.1, finally the Grade group 5 (Gleason scores 9 to 10 (4+5, 5+4, or 5+5) the HR was 12.7 compared to grade group 1

ISUP grade group classification system

Grade group	Gleason score and pattern
1	Grade 6 (3+3)
2	Grade 7 (3+4)
3	Grade 7 (4+3)
4	Grade 8 (4+4, 3+5, or 5+3)
5	Grade 9 or 10 (4+5, 5+4, or 5+5)

ISUP: International Society of Urological Pathology.

Adapted from: Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol 2016; 40:244.

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Table 5: ISUP grade group classification system (Klein, 2021)

Carter and colleagues reported in 2012 that the 5-year recurrence-free survival rates for grade groups 1, 2, 3, 4, and 5 were 95%, 83%, 65 %, 63%, and 35%, respectively (Carter et al., 2012).

In a prostate biopsy, there is no consensus on whether clinical therapy should be based on the highest score (grade group) of one component or the overall (global) Gleason score (grade group). If a Gleason 5 tumor component is found in a biopsy, such as in 3+5, 4+5, the highest score should be prioritized. When it comes to Gleason scores of 4+3, 4+4, or 3+4, the decision should be made on an individual basis, as the emphasis of these higher grades with 4 tumor components could be extremely modest (Yang, 2014).

2.8 Treatments

There are many types of PCa treatments available today, each with specific benefits and side effects. Only a thorough examination of the patient's features (age, life expectancy, etc.) as well as the disease (type, risk level) would allow the specialist to offer the most appropriate and individualized strategy, as well as to agree on the therapy based on preferences.

Professional society recommendations (Bekelman et al., 2018; Sanda et al., 2018) advocate for patient-clinician shared decision-making to help patients choose the treatment that best fits their personal beliefs. The most relevant advantages, drawbacks, and contraindications associated with each technique are outlined in **tables 6 and 7**.

The advantages of the main treatment options for early prostate cancer

External beam radiation therapy (EBRT)
Effective long-term cancer control with high-dose treatments
Very low risk of urinary incontinence
Available for cure of patients over a wide range of ages and in those with significant comorbidity
Brachytherapy
Cancer control rates appear equal to surgery and EBRT for organ-confined tumors
Quicker than EBRT (single treatment)
Available for cure of patients over a wide range of ages and in those with some comorbidity
Radical prostatectomy
Effective long-term cancer control
Predictions of prognosis can be more precise based on pathologic features in specimen
Pelvic lymph node dissection is possible through the same incision
PSA failure is easy to detect
Active surveillance
Reduces overtreatment
Avoids or postpones treatment-associated complications
Has no effect on work or social activities

PSA: prostate-specific antigen.

Modified from: Vogelzang NJ, Scardino PT, Shipley WU, et al. Comprehensive textbook of genitourinary oncology, 3rd Edition, Lippincott Williams & Wilkins 2005.

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Table 6: The advantages of the main treatment options for early prostate cancer (Klein, 2021)

The disadvantages of the main treatment options for early prostate cancer

External beam radiation therapy
Significant risk of erectile dysfunction
Lack of lymph node removed; late rectal symptoms more common than with brachytherapy or radical prostatectomy
Knowledge of possible metastasis to lymph nodes is not available
Up to one-half of patients have some temporary bladder or bowel symptoms during treatment
Brachytherapy
Significant risk of erectile dysfunction
Lack of lymph node removed; knowledge of possible metastasis to lymph nodes is not available
Up to one-half of patients have some temporary bladder or bowel symptoms with treatment; there may be exacerbation of preexisting lower urinary tract obstructive symptoms
Radical prostatectomy
Significant risk of erectile dysfunction
Risk of operative morbidity
Low risk of long-term incontinence
Active surveillance
Tumor may progress beyond the possibility for cure
Later treatment may result in more side effects
Living with untreated cancer may cause anxiety

Modified from: Vogelzang NJ, Scardino PT, Shipley WU, et al. Comprehensive textbook of genitourinary oncology, 3rd Edition, Lippincott Williams & Wilkins 2005.

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Table 7: The disadvantages of the main treatment options for early prostate cancer (Klein, 2021)

External beam radiation therapy (RT) with or without brachytherapy, brachytherapy alone, radical prostatectomy, or active surveillance are the basic options for PCa patients. The choice of one or more treatments is based on the cancer's clinical/pathological characteristics, as shown in **table 7.**

There are therapeutic options for patients with very low-risk disease characteristics and a life expectancy >10 years that allow treatment to be postponed until the disease becomes "clinically significant," initially performing only fairly frequent checks (PSA, rectal examination, biopsy) to monitor the disease's progression and control for any changes that require intervention ("active surveillance") (Bekelman et al., 2018; Sanda et al., 2018). However, this approach necessitates of close monitoring and may cause significant anxiety, leading many patients to select definitive intervention even in the absence of progressive disease.

Low-risk disease is defined as no palpable tumor in the prostate or restricted disease in one lobe of the prostate gland, a serum PSA of less than 10 ng/mL, and grading group 1 (Gleason score ≤6) disease (**Table 8**).

The choice of therapy is based on a well-informed patient decision that takes into account the potential benefits and disadvantages of various treatment options. Active surveillance or definitive therapy (radical prostatectomy or RT) for patients who have a high risk of progression on active surveillance are the standard therapeutic options for these patients (Bekelman et al., 2018).

External beam radiotherapy has been found to be effective in low-risk tumors, with results comparable to radical prostatectomy, in the treatment of PCa, in the treatments considered standard. In low-risk conditions, another radiotherapy treatment that appears to produce similar benefits to the others is brachytherapy, which involves inserting small "seeds" that deliver radiation into the prostate.

If the disease is confined to the prostate, radical prostatectomy, which involves the removal of the entire prostate gland as well as lymph nodes in region near the tumor, is considered a curative surgery. Because of significant advancements in surgical equipment, prostate removal surgery can now be conducted either traditionally (open retropubic radical prostatectomy) or robotically.

Patients with clinically localized, intermediate-risk PCa can have more extensive tumor in the prostate (e.g involving more than one-half of one lobe of the prostate [T2b] or with bilateral disease [T2c] on initial examination or imaging) but no detectable extraprostatic extension or seminal vesicle involvement. On initial examination or imaging, patients with clinically localized, intermediate-risk PCa may have a larger tumor in the prostate (e.g., involving more than half of one lobe [T2b] or bilateral disease [T2c]), but no detectable extraprostatic extension or seminal vesicle involvement. Radiation therapy (RT) and/or brachytherapy, as well as radical prostatectomy with pelvic lymph node dissection and active surveillance, are all alternatives for intermediate-risk patients.

Androgen deprivation therapy (ADT) is recommended as part of a combined modality strategy during RT because of the increased risk of recurrence or disseminated cancer. Patients should be warned that if active surveillance is undertaken, there is a larger risk of developing metastases than if final therapy is used. ADT works by lowering testosterone levels, which drive the growth of PCa cells. However, it has several negative side effects, including impotence, hot flashes, weight gain, osteoporosis, muscle mass loss, and fatigue.

Patients with clinically localized, high-risk PCa have a more advanced disease, as evidenced by the presence of assumed extraprostatic extension on digital rectal examination (T3a) or a serum PSA of less than 20 ng/mL or a grade of 4 or 5 (Gleason score 8 to 10). If the patient has a short life expectancy, the standard treatment options for these individuals are RT, radical prostatectomy with extensive pelvic lymph node dissection, or primary ADT alone.

Patients with locally advanced disease (T3b or T4), seminal vesicle involvement, tumor fixation, or invasion of neighboring organs are classified with a very high risk of progression or recurrence. Patients with a primary Gleason pattern of 5 (grade group 4 or 5) or 4 or more cores with a Gleason score of 8 to 10 (grade group 5) are also classified as very high risk. These individuals are at high risk of lymph node involvement, so they should all have a pelvic imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) done before starting treatment.

External beam RT with long-term ADT or radical prostatectomy with prolonged pelvic lymph node dissection are two treatment choices, especially for younger individuals.

Elderly patients or those with severe serious illnesses can choose not to apply any form of therapy and "wait" in some circumstances. This is what the Anglo-Saxons call "watchful waiting" or not providing therapies until symptoms manifest.

Patients with lymph node involvement according to the American Joint Committee on Cancer/ Union for International Cancer Control (AJCC/UICC) staging system classified as having stage IV (metastatic) illness (**Table 3 and 4**). Patients with lymph node metastases but no distant metastases are usually treated with definitive RT and ADT.

However, radical prostatectomy as part of a combination therapy that includes postoperative ADT and/or RT is a possibility for young individuals with minimal regional lymphatic spread suspected. In the case of disseminated metastases, and in those who are not candidates for definitive locoregional therapy but have a detectable or rising serum PSA following treatment, ADT with medical orchiectomy (using gonadotropin-releasing hormone) or bilateral orchiectomy is characteristically used. ADT may be used in conjunction with docetaxel chemotherapy in some cases.

Many new therapies are on the horizon for individuals with advanced stage PCa who are sensitive to castration (i.e., are resistant to the removal of male hormones through surgery or hormone therapy). These involve the use of new hormonal drugs that are not connected with older hormone therapy. Some of these therapeutic treatments will be available as new standard short-term treatment options in Italy. Chemotherapy, which is also associated with the use of earlier generation hormone therapy, is already accessible. This consists of a single medication administered intravenously (docetaxel).

In case of castration-resistant PCa and bone metastases, metabolic radiation is a treatment option generally proposed. This strategy is based on the ability of some radiopharmaceuticals, such as radium-223, to position themselves in places with significant bone "turnover" and deliver high-energy particles capable of destroying cancer cells to these locations.

There are some molecularly targeted therapies that have shown to be effective in clinical trials, including PARP (poly adenosine diphosphate-ribose polymerase) inhibitors, which can be used in men who have mutations in the BRCA genes, which are also involved in breast and ovarian cancer, and the new metabolic radiotherapy with 177Lu-PSMA-617. Immunotherapy has yet to show clear efficacy in these neoplasms. However, recent studies suggest that, particularly in the context of therapeutic combinations, this therapy may soon become an additional treatment for patients with cancer resistant to conventional therapies.

Risk stratification schema for localized prostate cancer, according to the National Comprehensive Cancer Network (NCCN)

Risk group	Clinical/pathologic features
Very low	▪ T1c AND ▪ Grade group 1 AND ▪ PSA <10 ng/mL AND ▪ Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core AND ▪ PSA density <0.15 ng/mL/g
Low	▪ T1 to T2a AND ▪ Grade group 1 AND ▪ PSA <10 ng/mL AND ▪ Does not qualify for very low risk
Favorable intermediate	▪ No high or very high risk features ▪ No more than one intermediate risk factor: • T2b to T2c OR • Grade group 2 or 3 • PSA 10 to 20 ng/mL AND ▪ Grade group 1 or 2 AND ▪ Percentage of positive biopsy cores <50%
Unfavorable intermediate	▪ No high or very high risk features ▪ Two or three of the intermediate risk factors: • T2b to T2c • Grade group 2 or 3 • PSA 10 to 20 ng/mL AND/OR ▪ Grade group 3 AND/OR ▪ ≥50% of positive biopsy cores
High	▪ No very high risk features AND ▪ T3a OR ▪ Grade group 4 or 5 OR ▪ PSA >20 ng/mL
Very high	▪ T3b to T4 OR ▪ Primary Gleason pattern 5 OR ▪ Two or three high-risk features OR ▪ >4 cores with Grade group 4 or 5

PSA: prostate-specific antigen.

Adapted from: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Prostate Cancer. Version 4.2018.

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Table 8: Risk stratification for localized prostate cancer, according to the National Comprehensive Cancer Network (NCCN) (Klein, 2021)

2.9 Toxicities and complications

Radiation therapy (RT; external beam and/or brachytherapy) is a common first-line treatment for men with clinically localized PCa. The goal of radiation therapy (RT) is to give a tumoricidal dosage of radiation while reducing radiation to the surrounding normal tissues (Pollack, 2000). The volume and anatomic distribution of both the tumor and the normal structures must be considered while planning RT (McLaughlin et al., 2005), because the prostate gland lies in close proximity to the rectum and bladder. The early and late consequences of radiation toxicity are highly reliant on the tissue treated, particularly the gastrointestinal and genitourinary systems.

Conformal RT techniques allow for higher doses of radiation to be delivered to the prostate gland than with earlier procedures. A daily dose of 1.8 to 2 Gy for 38 to 45 fractions is used in traditional RT programs utilizing highly conformal methods. Multiple studies have examined the impact of dose and found that dose escalation can help prevent biochemical failure after definitive RT.

External beam RT has a low morbidity rate in patients treated with modern procedures. The Radiation Therapy Oncology Group (RTOG) created a scale scales based on clinician reports to quantify acute and late treatment-related morbidity, as shown in **table 9** (Cox et al., 1995a).

Gastrointestinal toxicity. Enteritis or proctitis can occur frequently as a result of acute gastrointestinal toxicity during RT. Radiation proctitis incidence have been reported ranging from 5% to 30%, depending on the criteria used, the dose of radiation, and the treatment volume. Patients report abdominal cramps, urgency, tenesmus and defecation frequency. Antidiarrheal or topical anti-inflammatory medications are usually used to control them. Symptoms usually tend to resolve within 3 to 8 weeks after RT is finished. Long-term gastrointestinal side effects can occur in a small number of individuals and present as chronic diarrhea, tenesmus, rectal urgency or hematochezia (Haddock et al., 2007; Shipley et al., 1994). Strictures in the rectal or anal canals, fecal incontinence, ulceration, and perforation are uncommon. When highly conformal RT beams are employed and the dose to the rectum is limited, however, the rate of moderate to severe gastrointestinal symptoms found with high-dose RT techniques is comparable to that reported in men who receive lower RT doses (Zelefsky et al., 2001).

Urinary toxicity. Approximately half of patients have urine symptoms during external beam RT, which might include frequency, dysuria, and/or urgency owing to cystitis, urethritis, or both (Beckendorf et al., 2004; Dearnaley et al., 2005). Symptoms typically tend to resolve within four weeks after the completion of the therapy. Urinary tract complications in the late stages are uncommon. In men without a history of prior prostate surgery, the incidence of urine incontinence is probably around 1%, though this varies depending on the definition (Hamilton et al., 2001; Potosky et al., 2000, 2004). External beam RT may improve functional status in patients who had severe obstructive or irritative symptoms previous to treatment, possibly through reducing prostate size (R. C. Chen et al., 2009). Urinary strictures, cystitis, hematuria, and bladder contracture are some other long-term genitourinary toxicities (Elliott et al., 2007).

Sexual dysfunction. The frequency of erectile dysfunction in men treated with RT has been extensively studied. The frequency of new-onset impotence after external beam RT is influenced by the definition of potency and on the time frame of assessment (Talcott et al., 1998). In recent studies, 30% to 45% of males who were sexually active prior to RT became impotent after treatment, with the frequency increasing over time (Hamilton et al., 2001; Potosky et al., 2000).

Two years following external beam RT, a validated model has been built to predict the likelihood of erectile function. Planned neo-adjuvant hormone therapy (yes or no), pretreatment prostate-specific antigen (PSA) level (4 versus 4 ng/mL), and preoperative sexual health-related quality of life were all significant factors in this research (Alemozaffar et al., 2011).

Radiation-induced impotence may be caused by technical issues during RT delivery. According to the literature, avoiding penile structures (especially the corpus spongiosum) reduces significantly the risk of impotence greatly (Roach et al., 2010). In comparison to 3D-CRT, more advanced techniques of RT administration, such as IMRT, may limit the radiation to the penile bulb and corporal bodies (Buyyounouski et al., 2004).

Fatigue. Following RT, fatigue is frequent. In males with PCa, fatigue is evident prior to therapy and increases in frequency and intensity during treatment, according to prospective studies (Danjoux et al., 2007; Siddiqui et al., 2013).

Radiation Therapy Oncology Group (RTOG) criteria for long-term normal tissue toxicity

Symptoms
Diarrhea
Frequent loose bowel movements without associated rectal irritation
Proctitis
Rectal irritation or urgency, and the presence of mucous or blood in the stool, with or without frequent or sometimes loose bowel movements
Cystitis
Irritative bladder symptoms such as frequent dysuria; hematuria may or may not be a part of the clinical picture
Grades
Grade 0
No symptoms
Grade 1
Minor symptoms requiring no treatment
Grade 2
Symptoms that respond to simple outpatient management and do not affect lifestyle
Grade 3
Distressing symptoms affecting lifestyle; may necessitate hospital admission or minor surgical intervention (eg, urethral dilation)
Grade 4
Major surgical intervention or long stay in the hospital necessary (eg, laparotomy, colostomy, or cystectomy)
Grade 5
Fatal complications

Data from: Rubin P, Constine LS, Fajardo LF, Phillips TL, Wasserman TH. RTOG Late Effects Working Group. Overview. Late Effects of Normal Tissues (LENT) scoring system. Int J Radiat Oncol Biol Phys 1995; 31:1041.

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Table 9: Radiation therapy Oncology Group (RTOG) criteria for long-term normal tissue toxicity (Klein, 2021)

2.10 Microbiome, Microbiota and cancer

As reported by Berg (Berg et al., 2020), the microbiome is defined as a characteristic microbial community occupying a relatively well-defined habitat with specific physio-chemical features. The microbiome encompasses not only the bacteria involved, but also their activity theater, which culminates in the establishment of particular ecological niches. The microbiome, which is a dynamic and interactive micro-ecosystem that is subject to change in time and scale, is embedded in macro-ecosystems, including eukaryotic hosts, and is critical for their functioning and health. The microbiota consist of microorganisms from various kingdoms (Eukaryotes [e.g., Protozoa, Fungi, and Algae], Prokaryotes [Bacteria, Archaea]), and their "theatre of activity" includes microbial structures, metabolites, mobile genetic elements (e.g., transposons, phages, and viruses), as well as relic DNA embedded in the habitat's (Berg et al., 2020).

The interactions between the microbiota and the host have a significant impact on immunity and metabolism, and these interactions help to maintain host–microbe equilibrium homeostasis (Hooper et al., 2012; Nieuwdorp et al., 2014). Environment, lifestyle, smoking, age, food, prebiotics, antibiotics, and other factors can alter the balance and modulation of the gut microbiota. Using equipment such as next-generation sequencers and mass spectrometers, the examination of microbial genomes and metabolites of microbiota has become more accurate in recent years (Porter et al., 2018).

A large number of studies suggest that the gut microbiota is involved in disorders of other organs as well, including neurological, immunological and cancer diseases (Yu et al., 2021). In the last years, the influence of gut microbiota on cancer has received substantial attention based on findings that gut microbiota can be involved in all stages of cancer, including initiation, progression a and outcomes (Dzutsev et al., 2017). Therefore, according to current knowledge, gut microbiota diversity is an important element for a healthy gut environment and may explain disparities in the impact of diet and nutrition on cancer (**Figure 5**). Some recent studies suggest the potential influence of diet and nutrition on PCa and its partial mediation by gut microbiota, explaining a “microbiota-gut-prostate axis”.

The biological link between dysbiosis and PCa was recently supported by Massari et al. (Massari et al., 2019). They indicated that risk factors such bacterial and viral infections, proinflammatory microorganisms, and other environmental factors could play a role in PCa etiology. The gut microbiota produces metabolites that turn into proinflammatory cytokines, promoting chronic inflammation (Bingula et al., 2017).

Golombos and collaborators reported that the PCa cases had a higher relative abundance of *Bacteroides massiliensis* compared to controls, whereas the controls exhibited a higher relative abundance of *Faecalibacterium prausnitzii* and *Eubacterium rectalie* (Golombos et al., 2018) in a recent case-control study.

Cavarretta (Cavarretta et al., 2017) found that significantly more Staphylococcus species were present in tumor/peri-tumor tissues compared to non-tumor tissue, whereas Propionibacterium species were most abundant in all tested tumor/peri-tumor and non-tumor tissues in an analysis of the prostate tumor microenvironment.

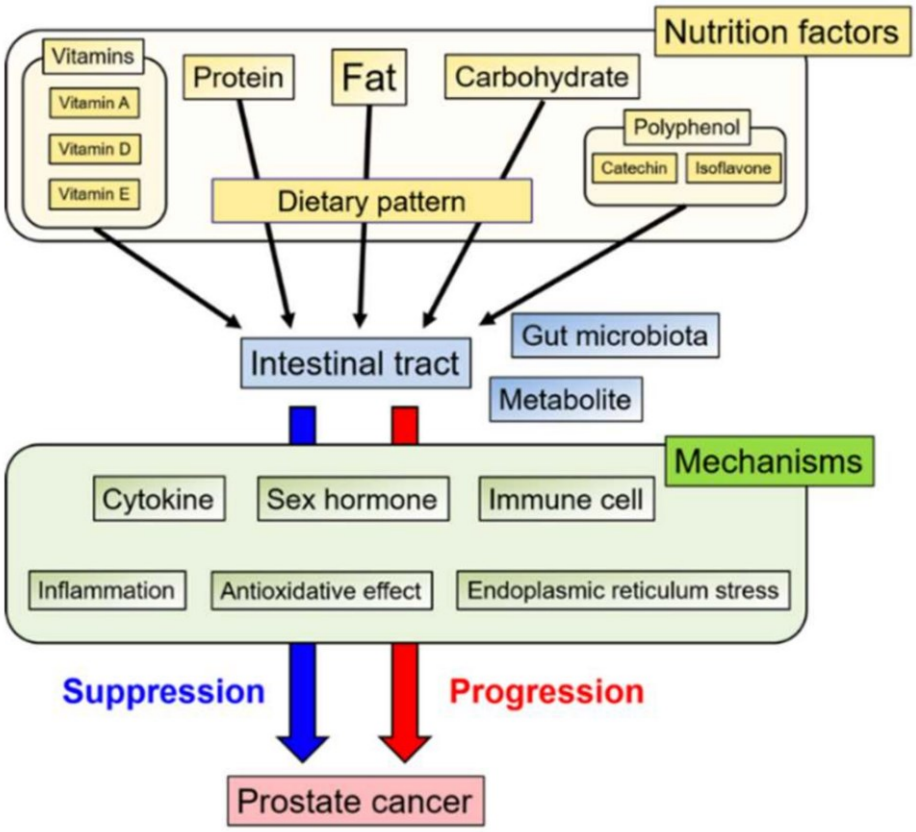

Figure 5. Various nutrition factors and mechanisms involved in the progression or suppression of prostate cancer via the intestinal tract (Dzutsev et al., 2017)

A study published in 2018 (Liss et al., 2018) studied the role of the gut microbiota of 133 patients undergoing prostate biopsies in the US. They found an association between the presence or absence of PCa and microbial composition. *Bacteroides* and *Streptococcus spp*. were significantly enriched in the gut microbiota of patients with PCa, with significantly altered folate and arginine pathways.

A recent study published by Li (J. K. M. Li et al., 2021) examined the GI microbiota of men undergoing treatment with ADT compared to patients with prostatectomy. They reported a significant difference in gut microbiome between PCa on ADT and prostatectomy. Men treated with ADT had lower GI microbial diversity (*Firmicutes*-to-*Bacteroidetes* ratio) and enriched biosynthesis of lipopolysaccharide (endotoxin) and propanoate. Both of them were associated with higher risk of developing metabolic syndrome and neurological complications. The authors hypothesize that GI microbiota profiles change upon ADT treatment but further studies are necessary to explore their relationship to the development of metabolic complications (Goudarzi et al., 2016).

Moreover, the commonly use of nonantibiotic drugs such as oral steroids, metformin, proton pump inhibitors (PPIs), antidepressants and seems to impact the composition and metabolic function of the GI microbiota (Vich Vila et al., 2020). Vich Vila et al. found that usage of laxatives, PPI and antibiotics can have an effect on the gut microbiome composition. Antibiotics inhibit bacterial growth, while laxatives and PPIs have an impact on the host. In particular the use of PPIs,

can impact the gut microbial composition changing the gastrointestinal pH, which promotes the growth of oral bacteria, and inhibiting certain commensal gut bacteria that include *Dorea* and *Ruminococcus* species.

Sfanos et al. (Sfanos et al., 2018), in a cross-sectional study of 30 patients, found significant differences in the gut microbiota composition of men taking oral androgen receptor axis-targeted therapies including bicalutamide, enzalutamide and abiraterone acetate. They reported a greater abundance of *Akkermansia muciniphila* and *Ruminococcaceae* species, which were previously linked to response to anti-PD-1 immunotherapy (Gopalakrishnan et al., 2018). The most widely used checkpoint inhibitors are monoclonal antibodies targeting programmed cell death protein 1 (PD-1) and its ligand PD-L1 (Routy et al., 2018).

It has not been elucidated the mechanisms by which gut microbiota is involved in PCa. The prostate gland is not an directly affected by gut microbiota, but it seems to be affected indirectly by cytokines and immune cells modified by microbiota in the gut or bacterial metabolites and components absorbed from the intestine that enter the systemic circulation. Further studies are needed to understand how changes in microbial composition had implications for overall health.

2.11 Primary, secondary and tertiary prevention

There are three basic types of prevention: primary, secondary, and tertiary. Primary focuses on prevention of incident disease in at-risk populations, secondary on attenuating the severity of prevalent disease through early detection and intervention, and tertiary on halting disease progression and recurrence in patients.

There is no specific primary prevention for PCa even if there are some lifestyle recommendations for potentially reducing cancer risk in adults according to the World Cancer Research Fund (WCRF) third Expert Report published in 2018 (WCRF/ AICR, 2018). These recommendations were based on a comprehensive meta-analysis of data published prior to 2018 that examined the impact of specific foods or food groups or individual nutrient supplements on the risk of occurrence of most cancers. Briefly, the recommendations specify that individuals should maintain body weight in the normal range, reduce sedentary lifestyle engaging daily moderate physical activity, consume daily quantities of fruits, no starchy vegetables, unprocessed grains, and legumes every day, and limit consumption of processed foods, sugar sweetened drinks, red meat, alcohol (WCRF/ AICR, 2018).

Other primary prevention consists in contacting the doctor and ask for urological examination every year, if you are familiar with the disease or if you have urinary discomfort and annually repeat PSA test.

Following PCa treatment, patients should undergo ongoing assessments for management of-related side effects, as well as preventive and general health care (Hewitt M, Greenfield S, 2005; Jacobs et al., 2009).

Follow-up for men on active surveillance should include repeat prostate biopsies, usually one year after the initial diagnosis and thereafter at predetermined intervals to look for signs of progression. The use of prostate MRI as a substitute for routine biopsy is increasing.

2.12 Side-effect, quality of life and Intervention trials for prostate cancer during radiotherapy

Both the diagnosis and treatment for PCa are extremely invasive and may causes feelings of depression and anxiety. Psychological research reported that diagnosis of cancer leads to feelings of uncertainty, loss of personal control, and feeling of powerlessness (Davison et al., 1995), can induce stress (e.g., financial, concerns, role changes) and increase personal vulnerability. In addition, the consequences of PCa and its treatment can produce long-term sequelae. Side-effects of treatment often can continue months or years after treatments affecting their quality of life (Galbraith et al., 2012; Ussher et al., 2016). Many years after treatment, patients report urinary and bowel dysfunction in addition to fear of recurrence (Bernat et al., 2016), and over 80% of patients cope with sexual dysfunction (Resnick et al., 2013).

Radiotherapy is a type of cancer treatment modality that uses beams of intense energy like ionizing radiation in order to kill the malignant tumor cells (De Ruysscher et al., 2019). During the treatment of tumors of the pelvic area the organ at high risk is the intestine. The cells at the base of the crypts of the gut mucosa, in particular during the S-phase of the cell cycle, are highly sensitive to ionizing irradiation due to their high proliferation rate (Rotten & Grant, 1998). In addition, radiation directed towards the intestines is believed to be deleterious to the mucosa because are involved also endothelial cells that supply the area with blood, and small thrombi are formed exacerbate further the vascular injury (Mihaescu et al., 2007). Moreover, the gastrointestinal tract injury can depend on different factors such as type of radiotherapy given, the dose delivered to tissues and how radiation energy dissipates through tissues (J. Andreyev, 2007).

Toxicity due to intestinal radiation can be categorized as **acute (early**) and **chronic (delayed**).

Acute toxicity generally occurs during the treatment (early) and consists of diarrhea, nausea, abdominal pain, rectal bleeding, bloating, and urgency which usually occur during the second week of the radiotherapy treatment and peaks within four to five weeks of the treatment (Khalid et al., 2006). Delayed/chronic toxicities occurs after the 3 months of the radiotherapy (delayed) (Hauer-Jensen et al., 2007) and consists of fecal incontinence, flatulence, urgency, abdominal pain and rectal bleeding which occurs after the acute symptoms or can occur on their own after the continued treatment with radiotherapy (H. J. N. Andreyev et al., 2012).

One of the methods to manage gastrointestinal symptoms induced by radiation is by modifying food consumption. **Dietary modification** are proposed to limit the acute inflammatory processes so that the subsequent fibrotic processes can be inhibited. Moreover, exposure to intestinal irradiation may result in severe damage to the intestinal villi, causing malabsorption.

Modification of food consumption after radiotherapy may help to reduce or eliminate undesirable changes in bowel habit. Different dietetic interventions have been suggested such as lactose and fat restriction, caffeine and fiber-containing foods that can reduced intake of motility stimulants (Andreou et al., 2021; Classen J, Belka C, Paulsen F, Budach W, Woffmann W, 1998; McGough et al., 2004). In order to achieve this, manipulation of fat, fiber, and lactose in diet is recommended. Low fiber content in food is preferred to reduce bloating. Lactose restriction is also advised during radiotherapy, as there is a damage to the mucosa of the intestine and hence breakdown of brush border enzymes, in this case, lactase. Many studies have proved that lactose and fiber-reduced diet have diminished the radiotherapy induced gastrointestinal toxicity in patients undergoing pelvic radiotherapy (Liu et al., 1997; Lodge et al., 1995; Resbeut et al., 1997; Salminen et al., 1988).

Elemental nutrition formula can be provided to patients which supplies proteins as peptides or amino acids, carbohydrates largely as maltodextrins and fats primarily as medium chain triglycerides (Capirci C, Polico C, Amichetti M, Bonetta A, Gava A, Maranzano E, Turcato G, 2000; Craighead & Young, 1998). Dietary restriction of some food items such as fat, fiber and lactose may help in reducing the grades of adverse events during the RT, but the conflicting dietary advice provided by the clinics reflect the lack of clear scientific evidence concerning the optimal diet for patients before, during and after radiotherapy.

Recently it has been proposed that the composition of the intestinal microbiota before pelvic RT may predict the outcome with regards to symptoms and the severity of both acute and late treatment (M. R. Ferreira et al., 2019a; González-Mercado et al., 2020; A. Wang et al., 2015a). Actually, some studies reported that radiation treatments induces dysbiosis and reduced microbial diversity in both mice and humans, with toxicity correlating to diversity and certain bacterial profiles (M. R. Ferreira et al., 2019a; González-Mercado et al., 2020; Y. Li et al., 2020; Mitra et al., 2020; A. Wang et al., 2015a). Gerassy-Vainberg et al. show that the transplantation of irradiated microbiota to germ-free mice increases their susceptibility to radiation injury and the irradiated microbiota stimulates the secretion of host IL1-b, which contributes to intestinal damage (Gerassy-Vainberg et al., 2018).

Moreover, during radiotherapy a gradual change in the microbiota have been reported for cancer survivors (Manichanh et al., 2008; Nam et al., 2013). The dysbiosis was reported to be more pronounced at 6 weeks post-irradiation than at 2 weeks post-irradiation, indicating that disruption/modification of the microbiome was not necessarily an acute event, but occurs gradually over time (Manichanh et al., 2008; Nam et al., 2013).

Despite the lack of clear evidence for the dietary strategy, it has been suggested that interventions aimed at improving intestinal health that are applied at an early stage, even prior to irradiation, can potentially reduce late occurring gastrointestinal dysfunction (Bull et al., 2021), 2021), but more definitive evidence and further exploration of the microbiota composition in a therapeutic role is required to inform dietary practice.

3 MICROSTYLE STUDY

3.1 Background and rationale

The fields of immunology, microbiology, nutrition, epidemiology and metabolism are rapidly converging, utilizing a new methodology to explain our intimate relationships with our microbial cohabitants.

Prostate cancer (PCa) is the second most common cancer worldwide and the fifth most common cause of cancer death among the male population (Sung et al., 2021).

PCa patients can be treated with hormone-, radiation- or chemotherapy and prostatectomy surgery, and these therapies often lead to a number of side effects such as urinary and erectile dysfunction, both acute and late toxicity and poor quality of life (Jereczek-Fossa et al, 2019). The standard non-surgical approach for localized PCa is radiotherapy (RT) (Jereczek-Fossa et al., 2019). The technological improvements of the last decades and the use of Intensity-Modulated Radio Therapy (IMRT) allowed reducing the amount of potentially toxic high doses to rectum and urinary

bladder (Jereczek-Fossa et al., 2019; Marvaso et al., 2018). However, the rate of acute Grade ≥2 rectal toxicity is about 20%. The 5-year Grade ≥2 risks for rectal bleeding, urgency/tenesmus, diarrhea, and fecal incontinence are 9.9%, 4.5%, 2.8%, and 0.4%, respectively (Delobel et al., 2017). Furthermore, increasing age, time since diagnosis and comorbidities amplify physical morbidity, poor symptom control, high perceived fatigue and in general a poor health-related quality of life (QoL), as well as psychosocial concerns (e.g., mood changes, distress)(Davis et al., 2014; Zajdlewicz et al., 2017).

There is evidence of salutary effects of intervention based on dietary changes and physical exercise able to improve quality of life (Keogh & MacLeod, 2012). Intervention based on exercise showed benefits on QoL, physical function, fitness and fatigue (Mohamad et al., 2015). Other studies suggest that nutritional intervention can have a positive effect on toxicities, weight loss and QoL (Croisier et al., 2021a; Isenring et al., 2003; Ravasco et al., 2003). No firm conclusion has been drawn on the efficacy of dietary modifications on GI toxicity outcomes (Andreou et al., 2021; Henson et al., 2013), but an individualized approach base on appropriate professional counselling to manipulate dietary intake based on emerging symptoms and needs throughout treatment is desirable (Wedlake et al., 2017). Moreover, nutritional status is pivotal to manage not only fatigue and quality of life (Baguley et al., 2017; Moyad et al., 2016) but also to reduce PCa-specific mortality (Peisch et al., 2017).

The **gut microbiota** and their metabolic products are in constant cross-talk with the host cellular metabolism. Recent studies have provided evidence on the regulatory role of microbiota in immunological responses and stress signaling, such as those observed after injury induced by ionizing radiation (Crawford & Gordon, 2005). It is known that the GI system is particularly susceptible to radiation injury, and the cytotoxic effects of radiation exposure can also lead to defects in the intestinal epithelial barrier, which offers higher permeability to luminal bacteria and triggers immune responses (Goudarzi et al., 2016).

Few studies investigated the association between microbiota and radiotherapy. Only few studies showed that radiotherapy-associated toxicity can be predetermined based on gut microbiota profile (Manichanh et al., 2008; A. Wang et al., 2015a).

Many pathologies related to autoimmune and inflammatory disorders arise from a failure to control misdirected immune responses against self, microbiota-derived, or environmental antigens. Vitamin D has been recognized as an immunoregulator, and this has led to investigations on the effect of Vitamin D supplementation in various autoimmune diseases and its anti-inflammatory effects.

Physical activity is positively associated with 25OHD among people with normal- and overweight BMI (Brock et al., 2010). Previous studies have shown that Vitamin D can affect the gut microbiome (Sun, 2018) and 25OHD, the indicator of the Vitamin D status (25OHD) and that VDR polymorphisms are associated with cancer risk, prognosis and mortality. Recent meta-analyses of clinical trials showed the effect of vitamin D on cancer mortality (Keum et al., 2019; Y. Zhang et al., 2019). Adiponectin, secreted by adipose tissue, exhibits insulin-sensitizing, anti-inflammatory, proapoptotic, and antiproliferative properties. Circulating adiponectin levels, which are determined predominantly by genetic factors, diet, physical activity, and abdominal adiposity, are decreased in cancer patients and they are associated with cancer prognosis, as we showed in previous meta-analysis and in a clinical trial(Macis et al., 2014, 2021).

No comprehensive analyses have been performed to investigate the influence of irradiation on gut microbiota in PCa patients and if diet and lifestyle may have a role in improving quality of life modifying microbiome and serum biomarkers.

Our hypothesis is that an early intervention based on personalized nutrition and physical activity advice can help cancer patients to protect the bowel from gastrointestinal side effects during radiotherapy (RT) and to manage to the best nutritional and psychological issues raising. We will provide strategies that offer moderate but prolonged protection throughout RT by limiting the acute and chronic inflammatory processes affording some protection against self-perpetuating fibrotic processes (Wedlake et al., 2017). Dietetic interventions alone based on restriction of lactose, fat, caffeine and fiber-containing foods (Classen J, Belka C, Paulsen F, Budach W, Woffmann W, 1998) have been suggested, but they are not enough. A personalized diet considering foods that are not too difficult to digest, with a controlled quantity and quality of fat, and to modulate the amounts of insoluble and soluble fiber should induce a radio-protective effect attenuating biliary and pancreatic secretions.

Thus, in this study a dietician and a physiotherapist will work together to motivate patients to adhere to indications and attenuating the psychological distress. These advices will be adapted and matched with international recommendation (Arends et al., 2017; WCRF/ AICR, 2018) during the 6-month intervention to ensure also positive long term effects (McGough et al., 2004).

This study will be also useful to understand causal mechanisms that may link diet and lifestyle with gastrointestinal side effects due to RT. Diet can re-shape gut microbiota and influence its function by modulating the production of metabolites (Song et al., 2020). This study aims to address the mechanism(s) by which microbiome may shape effect of the lifestyle intervention on both radiotherapy toxicities and efficacy.

The results of this innovative project will provide useful information for future intervention and potentially have a large public health impact in PCa survivors.

3.2 Aims

We aim to evaluate the effect of a 6-month intervention in a group of CPa patients undergoing RT. Intervention is designed to control side effects and to improve adherence to a healthy lifestyle (diet and increase level of physical activity and decreased sedentary time) measured by the change in adherence to a healthy lifestyle score. We will assess the impact of the intervention on toxicity and gastrointestinal symptomatology within a mediation framework analysis. This approach allows investigating how microbiome may mediate effect of treatment. We will also characterize the change in microbiome in relation to the change in cytokines/adipokines in association with early and late toxicity.

4 METHODS

4.1 Study design and participants

MicroStyle (**Micro**biota and life-**Style** in PCa patients undergoing radiotherapy) is a randomized two-arm crossover clinical trial (**Figure 6**). Study participants will be recruited among men undergoing RT in two centers (Milan and Naples). The study will be conducted over a three-year

period, during which patients will receive a 6-month intervention and will be followed for other 6 months. The crossover design is used to reduce drop-out and to offer all patients the same opportunities, and also to evaluate the effect of the intervention after 6-month from RT when patients should have recreated a healthier microbiome and have less treatment side effects.

In the first year, we will organize the intervention study and will start the patient's recruitment. In the second year, we will continue patients' recruitment and follow-up, and we foresee to end the study in the third year.

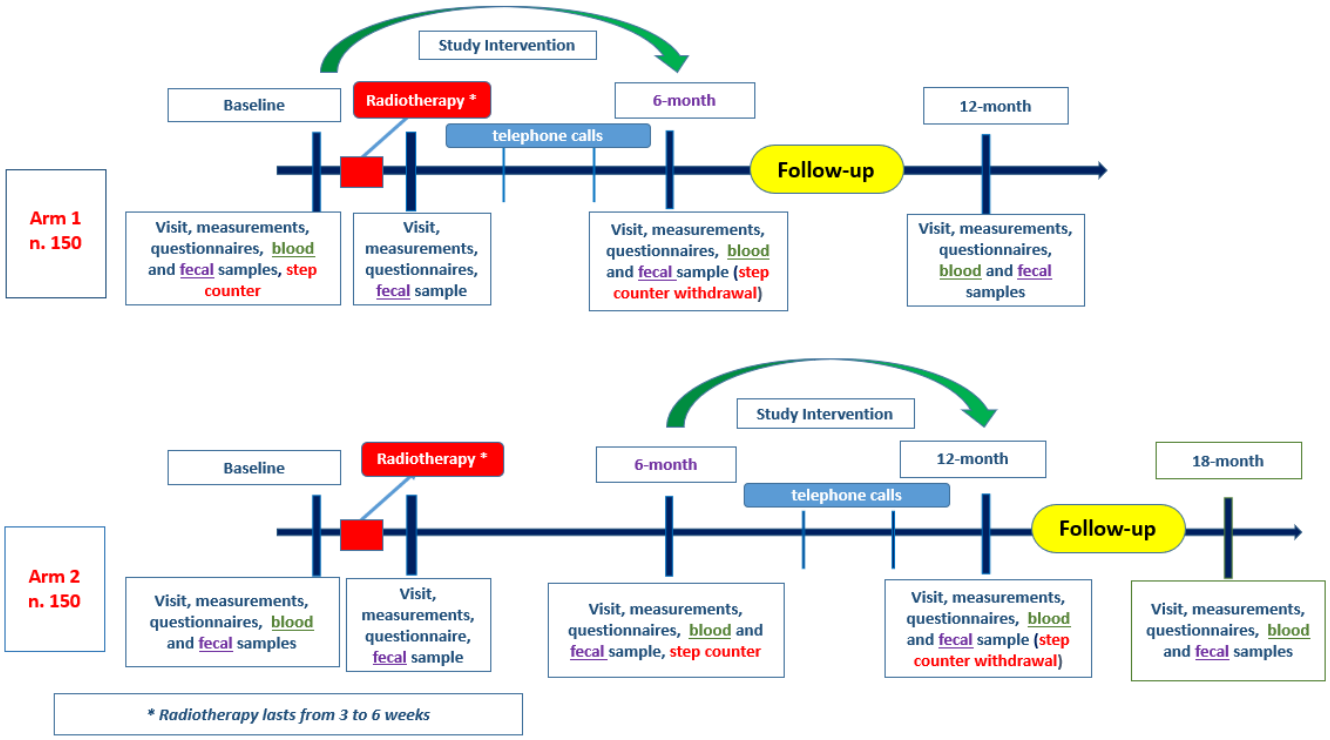

Figure 6: Study design

We foresee to randomize 300 patients over the study period in two intervention arms: Intervention Group (IG) and Control Group (CG). Participants allocated to the IG will meet a dietitian and a physiotherapist before RT to receive personalized diet and exercise recommendations, according to their health status, to improve overall lifestyle and reduce side effects (bowel and/or urinary problems). The dietitian will give indication to limit the gastrointestinal side effects reducing consumption of foods rich in fiber, lactose and simple sugars, and the physiotherapist will set individualized goals based on capabilities, lifestyle pattern and preferences to increase physical activity and to reduce sedentary time. Moreover, the physiotherapist will provide specific indication to improve genitourinary health to reduce urinary incontinence that follows prostate treatments, erectile dysfunction and pelvic pain due to muscle spasm.

All participants will be given a pedometer device (steps counter) in order to monitor and interfere (in the intervention group) with participants' physical activity and sedentary time. Participants included in the CG will receive at baseline general advice and materials available for patients undergoing RT. According to the crossover design, the CG will cross to the intervention as proposed for the IG, after the initial 6 months period (**Figure 7**)

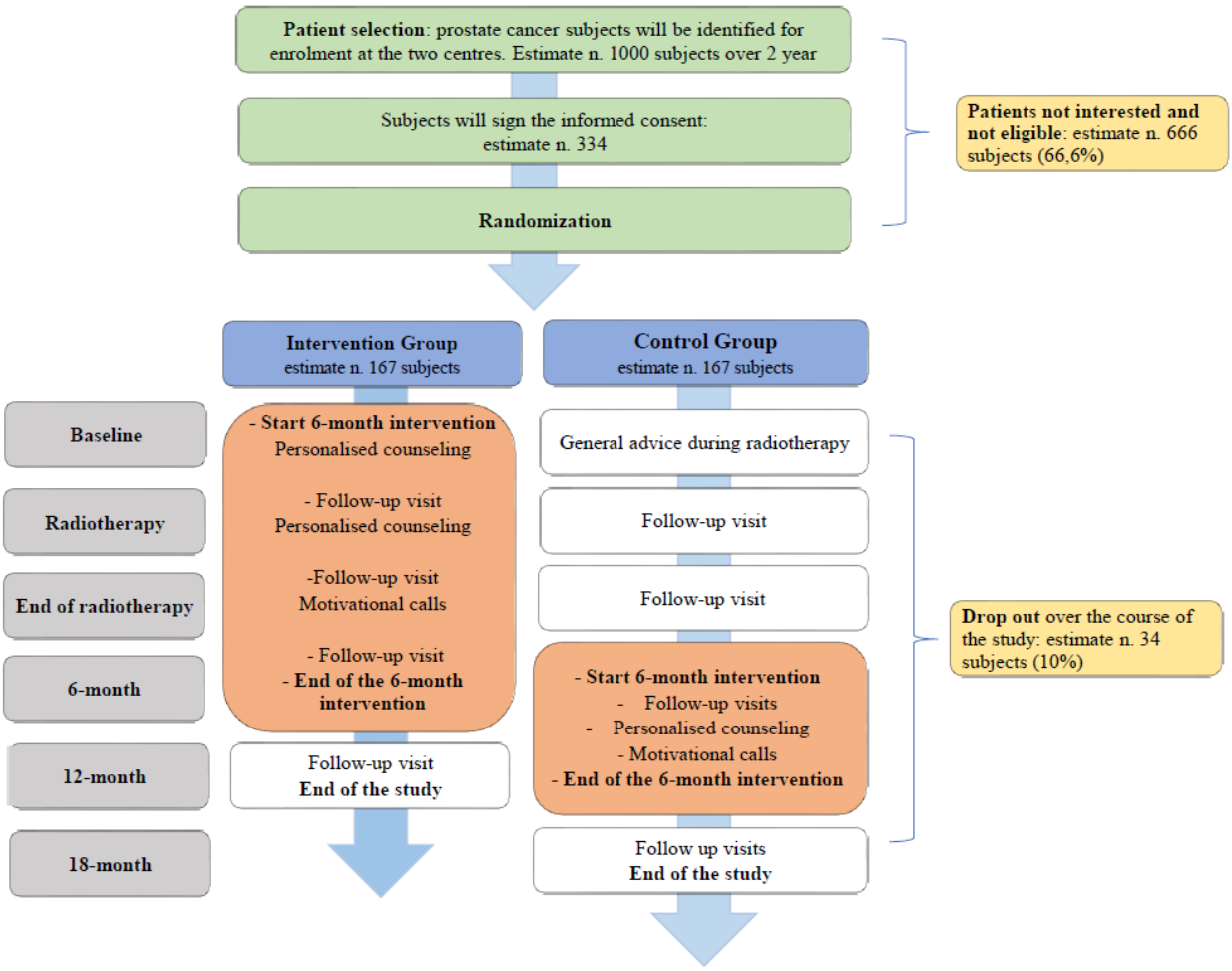

Figure 7. Flow chart

4.2 Study population and participants recruitment

Patients will be identified in the two centers among patients undergoing RT at the Division of Radiation Oncology at European Institute of Oncology (IEO), Milan and Department of Radiation Oncology, at the National Cancer Institute, "Fondazione G. Pascale", Naples. Cancer diagnosis and treatment status will be confirmed by medical record review. Potentially eligible participants will be contacted by a member of the investigation team who will explain the study. Those who express their interest in joining the study will then be approached by the research staff for further screening of eligibility. It is foreseen to enroll 334 patients (**Figure 7**) to obtain a final sample of 300.

4.3 Randomization

Randomization will be performed by a centralized computer process (Research Electronic Data Capture - REDCap® database platform) coordinated by IEO. Eligible participants will be randomly assigned in a ratio of 1:1 to either the two intervention arms (Intervention and control arm). Study arms will be balanced taking into account the proposed curative treatments (possible Androgen Deprivation Therapy (ADT) and surgery, pelvic lymph node involvements and centers.

4.4 Withdrawal and loss to follow-up

Individuals will have the right to withdraw consent for participation in any phase of the trial. Their medical care will not be affected at any time by declining to participate in or withdrawing from the trial. The research team will make every effort to minimize the loss to follow-up. If a participant misses one follow-up, we will try to re-arrange with them a session on at least two further occasions. The crossover design is used to reduce drop-out and to offer all patients the same opportunities.

4.5 Study procedures

Interventions will be delivered over a 6-month period and participants will be followed up for a further 6 months (**Figure 1**). Baseline assessment will be conducted by the team members. Measurements assessments will be made at 6-, 12- and 18-month after randomization only for the CG.

All participants will be followed over the study period. Depending on their allocated group, some participants will be contacted by telephone during the intervention period. Interventions will be delivered by trained staff and research team members.

4.6 Intervention

4.6.1 Intervention group (IG)

The goal of the intervention is to increase the quality of life of participants working on manipulation of habitual diet and level of physical activity that may help to reduce or eliminate bowel and/or urinary problems during RT.

Participants will meet a dietitian and a physiotherapist at baseline to receive personalized advice to prevent side effect according to their health status. The dietitian will give indication to limit the gastrointestinal side effects reducing/modifying consumption of foods rich in fiber-containing foods, lactose, fat and simple sugars (Bull et al., 2021; Classen J, Belka C, Paulsen F, Budach W, Woffmann W, 1998; Croisier et al., 2021b). A light diet will be suggested according to patient's dietary habits, along with individualized goals based on capabilities, lifestyle pattern and preferences to increase physical activity and to reduce sedentary time. Whether symptom remission has occurred, patient will be able to adhere to a more comprehensive and variable diet, based on World Cancer Research Fund (WCRF) recommendations (WCRF/ AICR, 2018). The physiotherapist will provide individualized indications to improve genitourinary health and to

advise about common RT side effect (Anderson et al., 2015; Centemero et al., 2010). Moreover, the physiotherapist will provide specific indication to improve genitourinary health and to advice the participant to search a specialized pelvic floor rehabilitation professional to reduce urinary incontinence, erectile dysfunction and pelvic pain due to muscle spasm. Depending on the individual characteristics, it will be encouraged to increase or to get a sufficient level of physical activity also walking at least 10.000 steps every day. Realistic level will be set to ensure compliance. Steps will be monitored over the study period by pedometers provided to the participants for daily use.

Three to four face-to face visits (depending on the cross-over design) and two telephone calls will be planned over the study period (intervention and follow-up) to monitor the adherence to the intervention, to support the participants and to provide personalized hint to deal with side effects (**Figure 2**). Individualized goals will be set for all participants included in the IG to reduce side effects and to improve quality of life. In the goal setting process workable solutions to problem encountered will be proposed. The contacts planned over the study intervention will ensure to monitor the patient compliance to the intervention.

The crossover design will provide us the possibility to evaluate the best timing (during vs after the end of RT) of the intervention in term of controlling side effects and to promote healthy lifestyle according to international guideline (Arends et al., 2017; WCRF/ AICR, 2018).

4.6.2 Content of the Intervention

Participants randomized to the IG will be offered an individualized counseling during cancer treatments that includes both a dietary and physical activity suggestions to control side effects, to cope with feelings of anxiety or depression and to improve quality of life.

The promotion of healthy behaviors will be initiate earlier than the standard care, to be more effective and last in the long term. Dietitian and physiotherapist will work together to set individualized goals to reduce or eliminate side effect and pain according to their health status. In particular, manipulation of habitual diet during radiotherapy (lactose, fat and fiber) are suggested to reduce diarrhea, abdominal pain, tenesmus or nausea which nevertheless detrimentally affect quality of life (Classen et al, 1998). Moreover, the physiotherapist will provide specific indication to improve genitourinary health and to advice the participant to search a specialized pelvic floor rehabilitation professional to reduce urinary incontinence, erectile dysfunction and pelvic pain due to muscle spasm (Anderson et al., 2015; Centemero et al., 2010). The physiotherapist will also provide hints to prevent and eventually manage the lymphedema of genitalia/lower limb for patients who underwent to pelvic lymph-node dissection, following the international recommendations ("The Diagnosis and Treatment of Peripheral Lymphedema: 2020 Consensus Document of the International Society of Lymphology," 2020). An adaptation of the recommendation to the patients' need and health status are more effective to engage men with PCa in healthy habits and improve their quality of life (Mohamad et al., 2015). These advices will be adapted and matched with international recommendation (Arends et al., 2017; WCRF/ AICR, 2018) during the 6-month intervention to ensure also positive long-term effects (McGough et al., 2004).

Lifestyle goals will use as reference the WCRF recommendations (WCRF/ AICR, 2018). Briefly, they specify that individuals should maintain body weight in the normal range, engage daily physical activity, eat vegetables every day, limit daily consumption of energy-dense foods, sugary drinks, red meat, and alcohol, and to be physically active as part of everyday life; to be moderately physically active, equivalent to brisk walking for at least 30 min a day; as fitness improves, to aim for ≥60 min of moderate or ≥30 min of vigorous physical activity every day; and to limit sedentary habits such as watching television, reading a book, playing pc games.

Reasonably, the initial goal will be to plan and implement daily purposeful mild to moderate exercise for a minimum of at least 10 min/day with a step-wise increase in time and intensity that was evaluated and modified once a week.

Individualized goals will be set for all participants. In the goal setting process workable solutions to problem encountered will be proposed. Each goal will be stated and included a concrete and verifiable outcome (reduction of fiber and alcohol, use public transportation/ or walking to go to the work instead of the car; use stairs instead of using the elevator).

4.6.3 Control group (CG)

Participants included in the CG will receive at baseline general advice and materials available for patients undergoing RT. According to the crossover design, the CG will cross to the intervention as proposed for the IG, after the initial 6-month period (**Figure 1** and **2**).

4.7 Study outcomes

4.7.1 Primary outcome

The primary outcome measure will be assessed at the end of the 6-month intervention:

- change in adherence to a healthy lifestyle score compared to the baseline.

4.7.2 Secondary outcomes

The secondary outcome measures will be assessed along intervention and included:

- change in PSA and serum biomarkers, insulin, testosterone, estradiol, sex hormone binding globulin (SHBG), hs-CRP, adiponectin, 25OHD, IL-6, LH compared to the baseline;
- change in blood lipid profile (total, HDL cholesterol and triglycerides) and glucose compared to the baseline;
- change in intestinal microbiome composition;
- change in body composition compared to the baseline, assessed at all visits using bioelectrical impedance vector analysis (BIVA);
- change in quality of life, measured by FACT-P questionnaire addressing the functional aspects of QoL and symptoms that commonly occur in PCa patients;
- change in food consumption measured at all visits using a short self-administered questionnaire;
- change in the level of anxiety during the study intervention;

- change in patient self efficacy, self-mastery and self-esteem during the study intervention;
- association between VDR polymorphisms, change in diet and serum biomarkers and microbiota composition;
- change in the level of physical activity levels and physical inactivity from baseline;
- change in acute and late toxicity, according to RTOG/EORTC scoring criteria;
- change in patient urinary function using international prostatic symptoms score (IPSS).

4.8 Selection and enrollment of participants

4.8.1 Inclusion Criteria:

- men aged 18 or older AND
- candidates for a prostate curative treatment with RT (which includes exclusive RT +/-hormone therapy, surgery followed by RT +/- hormone therapy) AND
- good performance status (ECOG < 2) AND
- written informed consent obtained AND
- willing to be randomized to either group, AND
- willing to wear the wrist-based activity monitor during the 6-month study period.

4.8.2 Exclusion Criteria:

- BMI <18.5 AND
- extra pelvic lymph node involvement or metastasis and severe medical condition(s) that would prevent optimal participation in the physical activities prescribed AND
- Malnutrition Universal Screening Tool (MUST) ≥ 2. It considers body mass index, weight change and acute disease effect equally and determines a malnutrition risk score. A score ≥2 identify a patient at high risk of malnutrition (Stratton et al., 2004) AND
- investigator does not approve participation in the study in case of severe clinical condition that would prevent optimal participation in the physical activities prescribed; any other severe medical condition or advanced age impeding the patient to adhere at the planned study follow-up period.

4.9 Measurements

Interventions will be delivered by trained staff and participants will be followed up to 12 or 18 months depending on the arm (IG or CG, respectively) (figure 1 and 2). The baseline visit will be organized concurrently with the simulation TAC used to set up RT. Data will be collected in person and prospectively at each visit as reported in **Table 10**. All questionnaires administered along the study are reported in **Appendices**.

ASSESSMENT	INSTRUMENTS	VISITS				
		Baseline	**After RT**	**T6**	**T12**	**T18§**
Height[1], weight, waist and hip circumference, Body Mass Index	Calibrated scales, stadiometer, tape measures	✓	✓	✓	✓	✓
Heart rate and blood oxygen saturation	Finger pulse oximeter	✓	✓	✓	✓	✓
Total, HDL, LDL cholesterol, triglycerides, glucose, insulin, PSA, and other serum biomarkers#	Blood Sample	✓		✓	✓	✓
Intestinal microbiome composition	Fecal Sample	✓	✓	✓	✓	✓
Body composition	BIVA (Bioelectrical Impedance Vector Analysis – Nutrilab device AKERN Srl – Italy)	✓	✓	✓	✓	✓
Food consumption	16-items Dietary Questionnaire	✓	✓	✓	✓	✓
Physical activity	International Physical Activity Questionnaire (IPAQ)	✓	✓	✓	✓	✓
Steps	Pedometer-like device (wrist band)	IG	-	CG	-	-
Quality of Life	Functional Assessment on Cancer Therapy (FACT-P)	✓	-	✓	✓	✓
Self-efficacy	Self-Efficacy Scale (GS-EF)	✓	-	✓	✓	✓
Anxiety	Anxiety Scale for Prostate Cancer (MAX – PC)	✓	-	✓	✓	✓
Life orientation	Life Orientation test (LOT-R)	✓	-	✓	✓	✓
Personality traits	Personal Traits Questionnaire (Con-OR)	✓	-	✓	✓	✓
Acute and late toxicity	Questionnaire acute and late toxicity - RTOG/EORTC*	✓	✓	✓	✓	✓
Erectile function	International Index of Erectile Function (IEEF)	✓	✓	✓	✓	✓
Urinary function	International Prostate Symptoms Score (IPSS), International Consultation on Incontinence Questionnaire (ICIQ-SF)	✓	✓	✓	✓	✓

Table 10. Study assessments.

4.9.1.1 Anthropometric measures

Weight will be measured at all visits, using a calibrated dedicated scale. Height will be measured at baseline. Height and weight will be used to calculate BMI (kg/m2).

4.9.1.2 Heart rate and blood oxygen saturation

Heart rate (HR) and blood oxygen saturation will be assessed with a finger pulse oximeter (Bongard, 1992; Hanning, 1995; Torp, 2021) in order to have a constant evaluation of patient's state and to plan a safe and tailored training program.

4.9.1.3 Blood sample

A fasting blood sample will be collected at each visits (except after radiotherapy) to measure PSA, insulin, testosterone, sex hormone binding globulin (SHBG), LH, and lipid profile (total, HDL, LDL cholesterol and triglycerides), glucose, hs-CRP, adiponectin, 25OHD. PSA, glucose and lipid profile will be analyzed on fresh blood sample as routinely done for these patients. Serum levels of insulin, and luteinizing hormone (LH), will be determined by a chemiluminescence microparticle immunoassay (CMIA). Serum concentrations of testosterone, 25-hydroxy-vitamin D, estradiol will be analyzed by chemiluminescence immunoassays designed for the IDS-iSYS Multi Discipline Automated System Analyser (Immunodiagnostic Systems Limited, UK). Adiponectin will be measured by an Enzyme linked immunoassay designed for the automated platform ELLA (ProteinSimple, Biotechne).

4.9.1.4 Fecal sample

Four/five fecal samples per patient will be self-collected by patients at each visits in a collection tube prefilled with preservative liquid to maintain the microbial DNA stability at room temperature, following the instructions delivered by staff member. Fecal samples will be further transported to IEO's laboratory, who is the responsible for all the downstream process of gut microbiota analysis. After amplification of V3-V4 16S rRNA DNA regions, samples will be sequenced using Illumina platform sequencer at IEO's laboratory. The related bioinformatic and statistical analysis will provide us the identification of the structure and composition of the microbial community, with the aim to identify a core microbiota related to the selected host treatment and/or the specific disease (Frugé et al., 2018). Moreover, the identification of the complete feces' metagenome will be performed by means of shotgun sequencing, improving taxonomic resolution and revealing at species level which are the specific taxa associated with the treatment and enteropathy. Finally, a correlation between variation in the luminal microbiota population and host metabolic pathway changes will be investigated.

4.9.1.5 Body composition

Body composition will be assessed at baseline and at all visits, using bioelectrical impedance vector analysis (BIVA) (Nutrilab device, AKERN Srl – Italy). BIVA is an accurate method for a quick measurement of body compartments (Buffa et al., 2014; Piccoli et al., 1994). The direct analysis of the two components of the impedance vector (Z), resistance (R, Ohm) and reactance (Xc, Ohm), allows a semi-quantitative evaluation of body composition in terms of body cell mass and hydration status. Data for total body water (TBW), body cell mass (BCM), extracellular water (ECW), fat-free mass (FFM), fat mass (FM) and percentage fat mass (% FM) will be available for all participants and will be used for identifying changes of fat and fat-free mass over the study period.

4.9.1.1 Food consumption

Food consumption will be measured at all visits using a short self-administered questionnaire (Gnagnarella et al., 2018) recently developed to assess adherence to the Mediterranean diet in the Italian population. In this contest, it will be used to record daily or weekly intake of the main food groups over the previous months and the change over the study (see **Appendices**). In this population, we decided to explore the consumption of dairy products, focusing also on cheese for the contrasting effect of different dairy products on cancer risk (i.e., protective for colon, risk for prostate) (WCRF/ AICR, 2018).

4.9.1.2 International Physical Activity Questionnaire

Physical activity will be measured with the IPA Questionnaire (IPAQ) at all visits. This questionnaire consists of questions that record the frequency and duration of mild, moderate, and strenuous exercise performed during free time in the previous 7 days. It measures physical activity and inactivity. It is a validated self-report measure of exercise that has been reliably used in previous studies (Craig et al., 2003). The total hours per week spent in each activity will be multiplied by the estimated metabolic cost of each activity (metabolic equivalent (MET) value) as determined from the Compendium of Physical Activities (Ainsworth et al., 2011) (Ainsworth et al., 2011).

4.9.1.3 Pedometer-like device

The intervention will propose a step counter (wrist band) that encourages both increased physical activity and decreased sedentary time. This device is able to record total steps taken, total distance traveled, total time active during the day and the greatest length of time of consistent movements done during the day. All participants will receive and will have to wear the wrist-based activity monitor during the 6-month intervention period. The IG from baseline to 6-month and the CG from 6-month to the 12-month. They could use a smartphone or a tablet application to get feedback on their activity and sedentary time.

4.9.1.4 Quality of life and health status and State-Trait Anxiety Inventory

The quality of life will be measured by FACT-P (Functional Assessment of Cancer Therapy – Prostate) questionnaire that contains scales and items addressing the functional aspects of QoL and symptoms that commonly occur in PCa patients. The 39-items questionnaire measures Physical, social/family, emotional, functional well-being, relationship with doctor, PCa symptoms on a 5-point scale (Esper et al., 1997).

4.9.1.5 Self-efficacy

An Italian adaptation of the General Self-Efficacy scale will be used to assess a general sense of perceived self-efficacy with the aim in mind to predict coping with daily hassles as well as adaptation after experiencing all kinds of stressful life events (Sibilia Lucio, 1995).

4.9.1.6 Anxiety

The level of anxiety will be measured at all visits using the Italian version of the Memorial Anxiety Scale for PCa (MAX-PC). This scale measures general anxiety and related to PSA levels, and fear of recurrence (Roth et al., 2003).

4.9.1.7 Life orientation test

The revised life orientation test (LOT-R) will be used to measure the mental disposition/attitude to optimism/pessimism. It is a 10-item questionnaire and respondents rate each item on a 4-point scale (Scheier et al., 1994).

4.9.1.8 Personality traits

Personality traits will be measured using a validated questionnaire (Mazzocco K, Masiero M, Monzani D, Milani A, Didier F, Pravettoni, n.d.). It consists of 34 items scored on a 5-point likert scale and provides information on 5 dimensions: control on self, self-oriented, need to be confirmed/seen, oriented on others, control on relationship and others' emotional protection (ConOR).

4.9.1.9 Acute and late toxicity

Acute and late gastrointestinal toxicities will be evaluated according to Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer (RTOG/EORTC) scoring criteria (Cox et al., 1995b).

4.9.1.10 Urinary function

The International Prostate Symptom Score (IPSS) will be utilized to measure the severity of lower urinary tract symptoms. It is a validated, reproducible scoring system to assess disease severity and response to therapy. The IPSS is made up of 7 questions related to voiding symptoms (Barry et al., 1992). The International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) is a tool for a subjective measure for evaluating the severity of urinary loss and condition-specific quality of life. The ICIQ-SF consists of four questions pertaining to the frequency of leakage, amount of leakage, interference with everyday life, and the perceived cause of leakage.

4.9.1.11 Erectile function

We will evaluate sexual function using the International Index of Erectile Function (IIEF). It is a widely used, multi-dimensional self-report instrument for the evaluation of male sexual function (Rosen et al., 1997).

4.10 Informed consent and privacy disclosure

At baseline visit, the purpose of the study will be explained to all eligible subjects and their consent obtained by a member of the investigation team. Only those who will have signed the informed consent form and the privacy disclosure will be included in the study (see **Appendices**).

4.11 Quality assurance

4.11.1 Identification of patients

According to good clinical practice (GCP) guidelines and current legislation, patients have a right to privacy (*Decreto Legislativo 30 Giugno 2003*, n.d.). Therefore, case report forms (CRF) or any other document related to the study will not contain subject names. Subjects will be identified by a unique code attributed at the moment of study inclusion. The IEO data manager will maintain the internal IEO registry for the identification of all IEO subjects participating in this study. The registry will contain:

- name and surname of the patient;
- medical record number;
- unique identification code;
- date of birth;
- date of inclusion in the study/signed informed consent.

Additionally, all institutional measures for the safeguard of patient privacy will be implemented.

4.11.2 Data Collection Forms

Each participant will have a personal card, containing all information, personal goals and personal status. It will be filled in by research staff.

All data collected on the questionnaires and all relevant information about the participants will be uploaded to the REDCAP platform. All forms must be filled in by the researcher or by a person delegated by the researcher, in accordance with the terms pertaining to authorized personnel.

All data will be treated with confidentiality, following the current privacy policy (*Decreto Legislativo 30 Giugno 2003*, n.d.).

4.11.3 Data Management

We will conduct the trial according to the International Conference On Harmonisation (ICH) Good Clinical Practice (GCP) guidelines (Dixon, 1999). Keeping accurate and consistent records is essential to a cooperative study. The IEO Data Management Office will responsible of the study database and data management. IEO Data Management Office, Direzione Scientifica, Istituto Europeo di Oncologia -Via Ripamonti, 435 - 20141 Milano - T 0257489938 F 0255210169 M 3356055650.

The methodology of collecting data will be done by software Redcap. Data for this study will be collected in a REDCap® (Research Electronic Data Capture) database. REDCap is a secure web platform for building and managing online databases and surveys. REDCap's streamlined process for rapidly creating and designing projects offers a vast array of tools that can be tailored to virtually any data collection strategy. REDCap provides an intuitive user interface that streamlines project development and improves data entry through real-time validation rules (with automated data type and range checks). REDCap also provides easy data manipulation (with audit trails for reporting, monitoring and querying patient records) and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). Investigators who have received appropriate institutional research approval (i.e., Institutional Review Board or Institutional Ethics Committee) will be given a web link with a survey where they can enter data about their specific patients. Guidelines about the data collection and to properly enter the data will be developed. The Promoter/Study Coordinator Centre is the legal owner of the collected data and has the right to manage it (including the data collected by the centers involved) in the case of a multi-site study, the sharing of data to any satellite centers is at the discretion of the Coordinator Centre under existing contractual agreements the regulation regarding protected health information (PHI) is also valid in Italy: it is therefore not possible to enter sensitive data of the subjects enrolled in the study or any other data (such as hospital codes/labels/SDO) that can lead to their identity; that's why when a subject is inserted into the platform, the system assigns it a unique identifier. The id/name-last name code decoding is the responsibility of the PI of each experimental center (and should not be shared with the Coordinator Center). Each experimental center will then be the only one to be able to decode the IDs assigned to the subjects managed by its center.

For experimental studies, the date of birth is usually encoded by keeping only month and year or year only according to the specifics of the study; observational studies should follow the same rule but it is "borderline" as dynamic, even today the actual date of birth is often collected without particular criticism by the regulators.

As for the timing of data retention, it depends on the contract you have with the server on which it is collected; all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines. More information about the consortium and system security can be found at http://www.projectredcap.org/.

Investigators will access the medical record of their patient, enter required data into the database. The protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project. Future research, which is not defined in this protocol, wishing to access the REDcap database will need institutional review board/ethic review board approval before obtaining access to the REDcap database.

4.11.4 Record retention

In compliance with the ICH/GCP guidelines (Dixon, 1999), the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s).

The investigator/institution will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained until at least 25 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 15 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor. If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

4.11.5 Participant rights and confidentiality

4.11.5.1 Informed Consent Forms

A signed consent form will be obtained from each participant. For participants who cannot consent for themselves, such as those with a legal guardian (e.g. person with power of attorney), this individual must sign the consent form. Please see **Attachments**: “Informed Consent”; “Consent for processing of personal data” (privacy disclosure).

4.11.5.2 Participant Confidentiality

All current legislation for the protection of privacy of participating subjects will be respected. To guarantee patient anonymity, all subjects will be identified by a code that will allow his/her identification solely by the clinical doctor responsible for his case, and by his collaborators. All files used for the collection or storage of patient data will be password-protected. The center of care will routinely apply all necessary measures to safeguard the reserved nature of clinical data.

4.11.6 Ethical considerations and study registration

Ethical approval has been obtained from the Ethics Committee of the European Institute of Oncology (Reference number: n. R1372/20 – IEO-1442) and of the National Cancer Institute, “Fondazione G. Pascale”, Naples (Prot. N. 2/21). The study will be conducted in agreement with the Helsinki Declaration and with current legislation in the matter of handling of personal data. The trial has been retrospectively registered on December 13, 2021 at the ClinicalTrials.gov (NCT05155618).

5 OUTCOMES AND STATISTICAL CONSIDERATION

5.1 Expected outcomes

We expect that our intervention will help to maintain fat-free mass, reduction of gastrointestinal side effects and an increase of physical activity levels. In general, we expect an improvement in quality of life and a reduction of the level of anxiety. We will also be able to evaluate whether the intervention will also improve microbiota diversity and reduce side effects of RT.

The crossover design is used to reduce drop-out and to offer all patients the same opportunities, and also to evaluate the effect of the intervention after 6-month from RT when patients should have recreated a healthier microbiome and have less treatment side effects.

The primary outcome measure will be assessed at the end of the 6-month intervention computing the score of adherence, using data collected at baseline and at the end of the first 6-month. We expect an increase of the score compared to the baseline.

The secondary outcome measures will be assessed along intervention during the follow-up visits:

- we expect and increased physical activity levels and reduced physical inactivity from baseline measured by the pedometer-like devices and from the IPAQ questionnaire;
- we expect an improvement in quality of life, reduction of the level of anxiety from baseline using the FACT-P;
- we will evaluate the effect of intervention on blood lipid profile (total, HDL cholesterol and triglycerides) and glucose compared to the baseline;
- we will evaluate the effect of intervention on some biomarkers: PSA and serum biomarkers, insulin, testosterone, estradiol, sex hormone binding globulin (SHBG), hs-CRP, adiponectin, 25OHD, IL-6, LH compared to the baseline;
- we will evaluate the effect of intervention on microbiome composition compared to the baseline;
- we will expect a reduction in acute and late toxicity, according to RTOG/EORTC scoring criteria;
- we will expect an improvement in patient urinary function using international prostatic symptoms score (IPSS).

5.2 Sample size considerations and main endpoint definition

Considering as main endpoint the percentage of adherent patients (defined as Healthy lifestyle score>4), a sample of 150 patients per arm will allow us to obtain a power of 80% and a 20% difference in the percentage of patients adhering to recommendation, assuming that in the intervention group the adherence is 40% under the null hypothesis and 60% in the alternative hypothesis. The hypotheses about frequency of adherence are based on results found in a previous study in a similar setting (Er et al., 2014; McCahon et al., 2015). The statistical test is a two-sided Z test with 'pooled variance'. The level of significance considered is 0.01 in order to take into account also multiple testing for exploratory analyses.

We will compute the score of adherence using BMI, physical activity and food consumptions, according to the standardized system (Shams-White et al., 2019). Briefly, we will use WCRF recommendations (WCRF/ AICR, 2018): they specify that individuals should maintain body weight

in the normal range, engage daily physical activity, eat vegetables every day, limit daily consumption of energy-dense foods, sugary drinks, red meat, and alcohol. We will assign participants a score based on quantitative cut-offs according to information collected during the baseline and the follow-up visits (BMI; level of physical activity; food consumptions). We will assign a score of 1, 0.5, and 0 for complete, partial, and non-adherence respectively. The score will range from 0 (minimal adherence) to 7 (maximal adherence).

Multivariate models (Lasso logistic model and Cox proportional hazard models) will be applied to investigate associations of changes in lifestyle, serum biomarkers and microbiome with quality of life and toxicity, taking into account False Discovery Rate (FDR) adjustment and confounding factors.

5.3 Statistical Considerations

In order to describe patients recruited in the study, descriptive statistics (median and interquartile range - IQR - for continuous variables; frequencies and percentages for qualitative ones) are reported by initial arm for demographic characteristics, baseline characteristics of the tumor and physical activity level. Shapiro-Wilk test was used for normality of data. Comparison of clinicopathologic characteristics among intervention group and control group were assessed using Mann–Whitney U tests for continuous variables and Chi-square or Fisher's exact test for categorical variables. Statistical significance was set at $p<0.05$. JASP 0.16.1 software was used to analyze the data.

The continuous IPAQ scores expressed as MET-minutes/week were calculated as the MET level (i.e. walking = 3·3 METs, moderate-intensity PA = 4·0 METs, vigorous-intensity PA = 8·0 METs) multiplied by the minutes of activity per week (Craig et al., 2003). The weekly PA levels as determined by the IPAQ scores were categorised into three levels according to the PA recommendations(Pate et al., 1995): **low** PA – <600 metabolic equivalent (MET)-minutes/week; **moderate** PA – at least 600 MET-minutes/week and **high** PA—vigorous-intensity activity of any combination of walking, moderate or vigorous activities that achieved a minimum of at least 3000 MET-minutes/week.

The Mediterranean diet score was calculated according to the validation study (Gnagnarella et al, 2018). It is assigned 1 point to participants reporting consumptions for each of the following foods that are characteristic of the Mediterranean diet above: vegetables (≥2/day), fresh fruits (≥2/ day), dried fruits (≥2/week), whole grain cereals (≥1/day), pulses (≥2/week), fish (≥2/week) and olive oil intakes (≥3/day). We also assigned 1 point to those consuming red and processed meat ≤1-3/week and 1 point for men drinking 1-2 glasses of wine per day (moderate consumption). The total score range from 0 to 9.

5.4 Planned analysis

In order to profile microbiome and genomics, we will identify microbial taxa, anywhere on the tree of life, that are over- or under abundant and associated with change in diet and lifestyle. We will use a variety of tools based on log-linear regression models with negative binomial or zero-inflated

Gaussian error models when dealing with counts data, and zero-inflated Beta models with relative data.

Regression estimates will be FDR-corrected to account for the multiple hypotheses testing problem. Multivariate models will be used to control for confounding effects or to test hypotheses of the microbiome as a mediator between exposures related to lifestyle or diet and health outcomes. Other multivariate approaches, including PCoA and PLS-DA analysis, will be carried out.

Alpha and Beta-diversity indexes differences will be compared using Wilcoxon rank test. We will employ the Data Integration Analysis for Biomarker Discovery (DIABLO) using Latent Components implementation in the mixOmics R package. The mixOmics block.splsda function will be used to identify the optimal number of components and taxa. We will also investigate how changes in time in beta-diversity is associated with change in diet and lifestyle. Because it is very challenging to find a suitable probabilistic distribution for the microbial data due to its unique features, such as zero-inflation, over-dispersion, complex correlation structure, and compositional nature (Lin et al., 2014; Tang & Chen, 2019), we will also carry out analyses based on the log-contrast model. In particular, the sparse linear log-contrast model (Lin et al., 2014); will be implemented to identify the taxa that are significantly associated with intervention, dietary factors or biomarkers. Taxa will be studied in the models also as response variables, as genetic association studies demonstrated that such inverse regression (treating dependent variables as covariates) is advantageous if there are multiple dependent variables and the distribution is difficult to specify (Majumdar et al., 2016). We will utilize the state-of-the-art compositional mediation analysis for microbiome data (R Package SparseMCMM) (Y. Li et al., 2020; C. Wang et al., 2020). The method enables us to estimate the total mediation effects of microbiome composition, as well as to select important microbial taxa mediating the diet-metabolite association and estimate taxon-specific mediation effects. Supervised heatmaps will be used to represent markers and taxa able to discriminate patients with good adherence to diet/lifestyle indications. We will report P-values and we will highlight associations that meet a FDR adjusted P-value less than or equal to 0.05 by the Benjamini and Hochberg method (J. A. Ferreira & Zwinderman, 2006).

5.5 Laboratory procedures

5.5.1.1 Collection, Handling and Shipping Procedures

Specific instructions about specimen handling and storage will be provided in a separate Manual of Operations and Procedures. Specimen collection kits for storage of serum and blood samples will be provided by the Central Laboratory, at the Division of Cancer Prevention and Genetics, European Institute of Oncology in Milan, Italy. A short leaflet containing the Instructions for requesting kits and Procedures for Storage of samples will be delivered. Briefly, they will provide labels and polypropylene cryotubes and rack (Thermo Fisher Scientific) and instructions for specimen handling, processing, labeling, tracking and storage.

The local site must be equipped with a -80°C (range -70 °C to -80 °C) freezer provided with temperature control 24 hours a day, 7 days a week and temperature log charts or an alarm monitoring system, better if electronic. The Center (Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Napoli) should also be equipped with a back-up freezer.

The Division of Cancer Prevention and Genetics, European Institute of Oncology in Milan, will also organize the pick-up of frozen blood and serum samples at the end of the study.

The stool sample will be transported to the laboratory in a plastic bag containing an ice pack within 7 days. Upon arrival in the laboratory each sample will be immediately homogenized and frozen -80°C for all analyses.

5.5.1.2 Blood sample analysis

Morning fasting blood samples will be collected between 8 and 11 a.m. Samples of whole EDTA-treated blood and serum samples for secondary endpoint biomarkers will stored at -80°C and analyzed in batches at the end of study. Also, peripheral blood mononuclear cells (PBMCs) will be isolated for a subset of patients from fresh EDTA-treated blood by centrifugation on Ficoll. Recovered cells will be then resuspended in freezing media (serum +10% DMSO) and stored at -80°C for future immunological assessments.

Serum concentrations of PSA, glucose and lipid profile (total cholesterol, HDL and LDH cholesterol, triglyceride), will be measured locally at each site on fresh blood samples at baseline and the end of the intervention as routinely done for these patients.

Samples of serum and whole EDTA-treated blood will be collected at baseline, while serum samples are collected three times. In the Intervention group, samples are collected and stored at baseline, after 6 months intervention and at 12 months. In the Control Arm samples are collected and stored at baseline, after 6, 12 and 18 months. We will measure adiponectin and IL-6 linked to inflammation and insulin resistance by using an automated platform for immunoassays (ELLA, ProteinSimple, Biotechne S.r.l. Italy). ELLA is a platform based on a microfluidic technology, that allows to perform automated immunoassays with very high sensitivity and low inter-assay coefficient of variation. Serum levels of hs-CRP, insulin and luteinizing hormone (LH) will be determined by a chemiluminescence microparticle immunoassay (CMIA) by the use of the automated platform ALINITY (Abbott S.r.l. Italy). Serum concentrations of testosterone will be analyzed by the Liason instrument (Diasorin S.p.r., Saluggia, Italy), 25-hydroxy-vitamin D, estradiol will be analyzed by chemiluminescence immunoassays designed for the IDS-iSYS Multi- Discipline Automated System Analyser (Immunodiagnostic Systems Limited, UK).

Genomic DNA will be extracted from EDTA treated whole blood specimens, by the use of QIAamp DNA blood kit (Qiagen, Valencia, CA) following the protocol of the manufacturer. For SNP determinations we will use the Applied Biosystems' Taqman Allelic Discrimination Assay (Foster City, CA, USA) according to manufacturer's instructions. Briefly, 10 ng of DNA is added to a reaction mix containing forward and reverse primers and two allele-specific fluorescent labelled probes (one wild-type and one variant allele specific). The polymerase chain reaction and fluorescence measurements will be performed using the ABI Prism 7000 sequence detection system. The following genetic polymorphisms of the VDR will be determined: FokI (rs10735810/rs2228570) BsmI (rs1544410), TaqI (rs731236) ApaI (rs 7975232), Cdx2 (rs 11568820) and promoter and the EcoRV of the VDR promoter (A-1012G) region. Furthermore, other polymorphism of genes involved in the vitamin D metabolism and activity (CYP27A1 rs703842, rs4646536, rs10877012, CYP24A1 rs2181874, rs2296241, rs4809958, rs6013905 and GC rs7041 and rs4588) will be determined.

5.5.1.3 Microbiome Analyses

Fecal samples will be collected for microbiome analysis at baseline and each subsequent time point. Specimens will be collected by patients at home and transported in a collection tube prefilled with preservative liquid, which stabilizes nucleic acids preventing them from being degraded up to 6-8 weeks at room temperature.

The stool sample collected in the Istituto Nazionale Tumori IRCCS Fondazione G. Pascale (Napoli) will be transported to the central laboratory in a plastic bag containing an ice pack within 7 days. Specimen collection kits for storage of fecal samples will be provided by the Nezi's lab European Institute of Oncology in Milan (IEO Campus), Italy (Luigi Nezi). A short leaflet containing the Instructions for requesting kits and procedures for storage of samples will be delivered. Briefly, they will provide labels and instructions for specimen handling, processing, labeling, tracking and storage.

Upon arrival at Nezi's lab (IEO Campus), each sample will be aliquoted and frozen 80°C until further processing. Microbial genomic DNA will be extracted from frozen samples using DNeasy PowerSoil Pro Kit (Qiagen) according to the manufacturer's instructions, then DNA will be quantified using a Bioanalyzer (Agilent Technologies, CA) and the V3-V4 hypervariable regions of the bacterial 16S rRNA gene will be sequenced on a MiSeq platform (Illumina), enabling taxonomic identification. Sequencing will be carried out at the Genomic Unit located at IEO Campus and all the data will be analyzed in Nezi's lab. The 250 bp 16S reads will be processed through QIIME2 (version 2019.7) (Bolyen et al., 2019) as follows: (1) Following visualization of demultiplexed samples and the average quality across the reads, quality filtering, dereplicating, and chimera filtering will be performed using the DADA2 (Callahan et al., 2016) plugin within QIIME2, setting the truncation length at 250 bp and the trimming by the length of the V3-V4 primer sequences (--p-trunc-len-f 250, --p-trunc-len-r 250, --p-trim-left-f 17, --p-trim-left-r 2, --p-trunc-q 2), and using consensus as the chimera filtering method; (2) a phylogenetic tree will be generated for downstream core diversity analyses using SATe'-enabled phylogenetic placement (SEPP) (Janssen et al., 2018), which first generates a reference tree—in this case using the SILVA 128 database (Gurevich et al., 2013) —then inserts 16S sequence fragments into the tree, thus achieving accuracy in phylogenetic tree reconstruction while retaining as much sub-OTU sequences as possible in the tree (3) alpha and beta diversity core metrics will be determined using the qiime diversity command, with the rarefaction depth set to the minimum sequence read output across the samples, after which statistical group comparisons of alpha and beta diversity metrics will be performed, using Kruskal-Wallis for alpha diversity and PERMANOVA for beta diversity; (4) taxonomy classification will be performed using the qiime feature-classifier classify-sklearn feature, using a Naïve Bayes classifier (Pedregosa FABIANPEDREGOSA et al., 2011) trained on SILVA 132 99% OTUs full-length 16S rRNA sequences (Gurevich et al., 2013), available from the QIIME2 website (https://docs.qiime2.org/2018.11/data-resources/). After filtering the feature count table for unassigned reads and setting a prevalence filter of >50% of the samples, the tables will be collapsed to each taxonomic level (kingdom, phylum, class, order, family, genus, species) and will be exported for further analysis in R. Differential abundance analysis will be performed on the raw counts table using DESeq2 (Love et al., 2014), Statistical significance of log2 fold changes will be assessed using the default Wald test with Benjamin-Hochberg p-value correction in

DESeq2. Cut-off for all significance tests was set at $P < 0.05$. Amplicon-based metagenomic approach represents one of the best strategy to obtain a largescale assessment of the taxonomic content of complex samples while containing costs.

6 RESULTS

6.1 Preliminary results

The recruitment of trial participants started in October 21, 2021 at the Division of Radiation Oncology of the European Institute of Oncology (IEO), Milan and in January 22, 2022 at the Department of Radiation Oncology of the National Cancer Institute, "Fondazione G. Pascale", Naples. Radiation oncologists confirmed cancer diagnosis and treatment status. A signed consent form was obtained from each participant who were randomized through the REDCAP platform. As of March 10, 2022, 27 men were enrolled in the trial in the two centers, 20 in Milan and 7 in Naples (**Figure 8**).

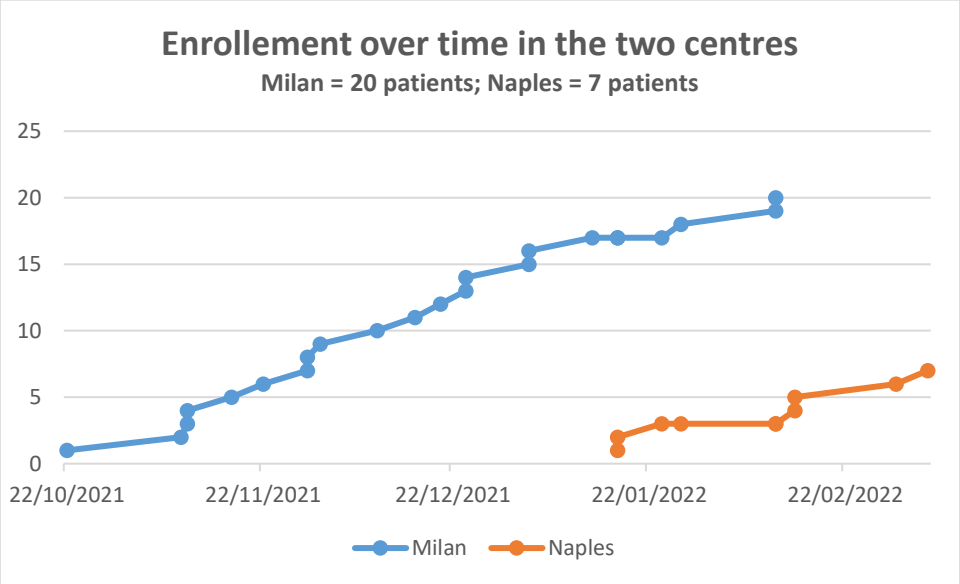

Figure 8. Enrollment over time in the two study centers (Milan and Naples) (n. 27 patients on March 10, 2022)

Following the study procedures, all participants received a link by mail generated by the REDCAP platform to fill in the study questionnaires. During the following visits, the staff checked all questionnaires for completeness and possible inconsistences or errors to provide quality assurance. All data collected at the baseline and follow-up visits were uploaded to the REDCAP platform.

Twenty-six patients (96.3%) completed the baseline visit, the study questionnaires and had their biological specimens (fecal and blood) correctly collected and stored. As reported in Table 12, participants median age is 70.5 years (inter-quartile range [IQR] 10.5) with a median BMI of 27 (IQR 45) and a median WHR ratio of 1.01. 65% of participants are active workers, 77% are married, 19% are current-smokers and 50% ex-smokers. Self-reported concomitant diseases were registered at the time of the survey and are listed in **Table 12**. Cardiovascular diseases (73%),

gastrointestinal diseases (42%) and bone diseases (38%) are the most frequent. Participants characteristics were similar in the two study centers.

	All (n=26)	**IG (n=15)**	**CG (n=11)**	
Characteristics	*Median (IQR)*			*p-value§*
Age (years)	70.5 (10.5)	70.5 (8.75)	71.5 (10.75)	0.79
Body weight (kg)	79.5 (14.25)	82.3 (13.9)	74.4 (9.25)	0.50
BMI (kg/m2)	27.5 (4.97)	27.8 (4.94)	27.3 (3.23)	0.22
WHR	1.01 (0.06)	1.01 (0.07)	1.00 (0.06)	0.30
Heart rate (Bpm)	84 (24)	80 (27)	85 (17)	0.78
Perfusion (Bpm)	96 (3)	96 (2.5)	96.5 (2.5)	0.75
Mediterranean Adherence score	4 (2)	3 (4)	5 (3)	0.25
Degree of education	**n (%)**			0.92
None	1 (4)	1 (7)	0 (0)	
Primary	9 (35)	6 (40)	3 (27)	
High school	12 (46)	6 (40)	6 (55)	
Graduate/postgraduate	4 (15)	2 (13)	2 (18)	
Occupation				0.23
Active	17 (65)	8 (53)	9 (82)	
Retired	8 (31)	6 (40)	2 (18)	
Marital status				1.00
Married or cohabiting	20 (77)	12 (80)	8 (73)	
Separated or divorced	4 (15)	2 (13)	2 (18)	
Widow	2 (8)	1 (7)	1 (9)	
Smoking status				0.76
Current	5 (19)	2 (13)	3 (27)	
Ex-smokers	13 (50)	8 (53)	5 (45)	
Never	8 (31)	5 (33)	3 (27)	
Concomitant diseases*				
CVD	19 (73)	11 (73)	8 (73)	1.00
Diabetes or hyperglycemia	4 (15)	1 (7)	3 (27)	0.28
Gastrointestinal disease	11 (42)	6 (40)	5 (45)	0.78
Bone diseases	10 (38)	6 (40)	4 (36)	1.00
Neurological diseases	1 (4)	1 (7)	0 (0)	1.00
Other neoplasms	4 (15)	3 (20)	1 (9)	0.61
Other diseases	14 (54)	9 (60)	5 (45)	0.46

*Patients may report more than one pathology; §Differences between categorical variables were evaluated by Fisher exact test or Chi-square. Differences between continuous variables were studied by Mann-Whitney U test.

Table 12. Patient characteristics at baseline.

Prostate cancer characteristics of the enrolled patients are reported in **Table 13**. In respect to the inclusion criteria, they present a low to moderate cancer risk as reported by ISUP grade and risk stratification by NCCN, 2020. Previous cancer treatments are reported in **Table 14**. Primary cancer were not treated (active surveillance) in 23% of the sample. Respectively 12% and 8% were

treated by hormone therapy alone or treated surgically with other treatments. Twenty-three percent of the sample were treated surgically for a biochemical relapse. Overall, we observed no significant difference between groups (P>.05), due to the small sample size and randomization procedure. We found a significant difference only for the Gleason Score (p=0.02) (**Table 13**), which is attributable to chance.

Cancer characteristics*	**All (n=19)**	**IG (n=13)**	**CG (n=6)**	
	n (%)			*p-value§*
Clinical T stage#				0.51
cT1	11 (58)	8 (62)	3 (50)	
cT2	5 (26)	4 (31)	1 (17)	
cT3	3 (16)	1 (8)	2 (33)	
Clinical N stage^				0.35
cN0	16 (94)	11 (100)	5 (86)	
cN1	1 (6)	0 (0)	1 (14)	
Clinical M stage ç				0.35
cM0	10 (53)	5 (38)	5 (83)	
Gleason score				0.02
6	4 (21)	4 (31)	0 (0)	
7	12 (63)	9 (69)	3 (50)	
8	1 (5)	0 (0)	1 (17)	
9	2 (11)	0 (0)	2 (33)	
ISUP§ grade				0.12
1	4 (26)	4 (31)	0 (0)	
2	9 (53)	6 (46)	3 (75)	
3	3 (18)	3 (23)	0 (0)	
5	1 (6)	0 (0)	1 (25)	
Risk stratification by NCCN $ 2020				0.52
Low	3 (16)	3 (23)	0 (0)	
Intermediate favorable	8 (42)	6 (46)	2 (33)	
Intermediate unfavorable	3 (16)	2 (15)	1 (17)	
High	5 (26)	2 (15)	3 (50)	

Clinical T stage: Clinical Tumour stage; ^ Clinical N stage: Clinical lymph Nodes stage; ç Clinical M stage: Clinical Distant Metastasis stage; § ISUP: International Society of Urological Pathology; $ NCCN: National Comprehensive Cancer Network; *missing data for CN and cM; Fisher's exact test for categorical variables.

Table 13. Prostate cancer characteristics of the enrolled patients.

	All (n=19)	**IG (n=13)**	**CG (n=6)**	
Primary cancer	*n (%)*			*p-value§*
None (Active surveillance)	6 (23)	2 (13)	4 (36)	0.56
Hormone therapy alone	3 (12)	3 (20)	0 (0)	
Surgery + adjuvant treatments	2 (8)	1 (7)	1 (9)	
Biochemical relapse (surgery)	6 (23)	3 (20)	3 (27)	
Missing data	5 (19)	3 (20)	2 (18)	

Fisher's exact test for categorical variables.

Table 14. Prostate cancer treatment.

Physical activity measures at baseline using the IPAQ questionnaire are reported in **Table 15**. Total MET's/week reported as median and IQR is 1059 (3900). So far, patients randomized to the CG reported a higher total METs/ week compared to patients in the IG, although no statistical significant difference between the two groups was found. Based on categories defined by ACSM, respectively 32%, 40% and 28% of participants in the total sample reported low, moderate and high physical activity levels.

	ALL (n=25)	**IG (n=14)**	**GC (n=11)**	
MET's/week	*Median (IQR)*			*p-value§*
Walking	198 (693)	198 (314)	347 (594)	0.89
Moderate activity	0 (840)	0 (600)	0 (960)	0.75
Vigorous activity	0 (900)	0 (970)	480 (960)	0.14
Total METs/week	1059 (3900)	832 (2781)	1752 (3966)	0.15
Sitting min/day	240 (240)	210 (300)	300 (240)	0.25
Physical Activity Level	*n (%)*			0.53
Low	8 (32%)	5 (36%)	5 (45%)	
Moderate	10 (40%)	6 (43%)	2 (18%)	
High	7 (28%)	3 (21%)	4 (36%)	

*§*Qualitative variables were analized by Fisher exact test. Quantitative variables were analized by Mann-Whitney U test.

Table 15. Metabolic equivalents (METs) and level of physical activity measured by international physical activity questionnaire (IPAQ)

Table 16 presents responses to the 16 items of the short questionnaire on adherence to the Mediterranean diet, indicating food consumption at baseline. We highlighted responses ≥39% in bold blue and in green (cells) the frequencies in agreement with national recommendations (AAVV, 2018).

The participants reported a consumption in line with the recommendation for fruits (2 portion per day=61%), wholegrains bread and substitutes (1-2 portion per day=39%), red meats (1-3 portion per week=43%), white meats (1-3 portion per week=61%), cheese (1-3 portion per week=57%), butter (seldom=70%) and sweetened beverages (seldom=65%). They do not meet recommendations for wholegrain pasta or rice, vegetables, fish, dried fruit, sweets, pastries, biscuits and pulses.

Food Items	Never seldom	<1 per day	1 per day	2 per day	≥3 per day
1. Wholegrain pasta or rice	**43%**	22%	30%	4%	0%
2. Vegetables, all types (raw and cooked)	0%	22%	**43%**	30%	0%
3. Fruits, all types fresh and fresh juices	13%	4%	22%	**61%**	0%
4. Milk and yoghurt	**43%**	9%	**48%**	0%	0%
	Never seldom	**<1 per day**	**1-2 per day**	**3-4 per day**	**≥5 per day**
5. Wholegrain bread and substitutes	35%	17%	**39%**	9%	0%
6. Olive oil to cook and to dress	0%	9%	**65%**	26%	0%
7. Butter, margarine or cooking cream	**70%**	17%	13%	0%	0%
8. Wine (white and red)	22%	35%	30%	13%	0%
	Never seldom	**<1 per week**	**1-3 per week**	**4-6 per week**	**≥7 per week**
9. Red meat (beef, veal, pork), meat products	17%	30%	**43%**	9%	0%
10. White meat (chicken, turkey, rabbit)	4%	35%	**61%**	0%	0%
11. Fresh and aged cheese	4%	26%	**57%**	13%	0%
12. Carbonated and/or sugar-sweetened beverages	**65%**	13%	17%	4%	0%
13. Manufactured sweets, pastries, biscuits, creams...	26%	26%	30%	17%	0%
	Never seldom	**<1 per week**	**1 per week**	**2-3 per week**	**≥4 per week**
14. Fish (fresh or frozen) or sea foods	9%	13%	**43%**	30%	4%
15. Dried fruits (nuts, almonds, hazelnuts)	22%	22%	26%	26%	4%
16. Pulses (chickpeas, lentils, peas, beans)	9%	30%	22%	35%	4%

Table 16: Responses in percentages (bold blue) to the 16 items questionnaire by participants at baseline. The highlighted cells in green are the Italian recommended frequencies of consumption by single food group (CREA; 2018).

7 DISCUSSION AND CONCLUSIONS

The present thesis reports preliminary data collected for the Microstyle intervention trial. The presented study is focused on dietary and physical activity counselling in a group of men undergoing RT for PCa in two Italian centers (Milan and Naples). This randomized- two-arm crossover trial is innovative in its design because we proposed the combined effect of dietary and physical activity counselling on patients undergoing RT, to control side effects and to cope with feelings of anxiety or depression. The intervention is initiated earlier than in the standard of care, i.e. before the beginning of the RT. Men with PCa have been reported to experience distress for side effects. Both the diagnosis and treatment of PCa are extremely invasive and may cause feelings of depression and anxiety. Cancer diagnosis can induce stress (e.g., financial, concerns, role changes) and increase personal vulnerability. Men with PCa can experience feelings of uncertainty, loss of personal control and powerlessness (Davison et al., 1995). Men are less likely to discuss their physical or psychological concerns with health professionals and they avoid seeking psychological support (Forsythe et al., 2013). As reported by Fang (Fang et al., 2020), PCa patients are more likely to experience isolation and poor social functioning, and this can result in more physical and psychological-related unmet needs.

Acting on a successful process of engagement in healthy lifestyle behaviors can boost the effects of interventions and allow long-term results. This study aims at a holistic approach where not only the organ is considered but the patient in its complexity. The intervention also aims to ensure that the concern is lowered and the patient learns to take care of himself with a better lifestyle.

Despite the lack of clear evidence for particular **dietary strategy**, the intervention aims at improve intestinal health at an early stage, to be more effective and last in the long term potentially reducing late-occurring gastrointestinal dysfunction. A recent important meta-analysis (Crowley et al., 2019) showed that medical students are not supported to provide high-quality, effective nutrition care. This study will outline the importance of training and knowledge of nutrition in cancer management. We expect an improvement in quality of life and a reduction of the level of anxiety. We will propose specific approach such as goal setting, self-monitoring of behavior and prompt follow-up will help to reducing drop-out. The crossover design will provide us the possibility to evaluate the best timing (during vs after the end of RT) of the intervention in term of controlling side effects and to promote healthy lifestyle according to international guideline (Arends et al., 2017; WCRF/ AICR, 2018).

Previous systematic reviews and meta-analyses demonstrated that **exercise intervention** for PCa patients improved cardiovascular fitness, fatigue, quality of life and social and cognitive functioning (Bourke et al., 2016; Fang et al., 2020; Menichetti et al., 2016). Combining aerobic and resistance training, PCa survivors are most likely to experience a small beneficial decrease in TNF and CRP, pro-inflammatory markers (Khosravi et al., 2019).

Our intervention does not foresee any structured physical activity, but it will take advantage of a pedometer device to quantify the level of activity by means of a common and easily understood metric (i.e., steps). This device is appealing since it objectively monitors physical activity and can be an important means for providing behavioral feedback and motivation (Bravata et al., 2007; Kang et al., 2009; McMurdo et al., 2010). Pedometer-based walking interventions have demonstrated their effectiveness in increasing physical activity in adult populations (Singh et al., 2021).

MicroStyle trial will provide important insights regarding the role of the **microbiome** and its interaction with serum biomarkers on the association with side effects of RT. We would like to carry out a comprehensive molecular analysis to investigate the influence of irradiation on gut microbiota in PCa patients. We will also expect to evaluate whether the intervention will provide microbiota diversity and reduce side effects of RT. In addition, the 6-month follow-up allows the evaluation of the effect of the intervention when patients should have recreated a healthier microbiome and have less treatment side effects.

It has been well demonstrated that the gut microbiota may contribute to the pathogenesis of radiation enteropathy and how it presents opportunity to predict, prevent or treat radiation enteropathy, but there is paucity of clinical studies on PCa patients. The intestinal microbiota before pelvic radiotherapy seems to predict the outcome with regards to treatments-induced symptoms (M. R. Ferreira et al., 2019b; A. Wang et al., 2015b). Moreover, radiation induces dysbiosis and reduced microbial diversity, with toxicity correlating to diversity and certain bacterial profiles (Y. Li et al., 2020; Mitra et al., 2020). Knowledge of the interaction between lifestyle, microbiome and serum biomarkers may lead to improved personalized cancer medicine and the development of targeted interventions. There is the need for evidence regarding the most effective approach in promoting healthy dietary habits and lifestyle in patients undergoing RT for PCa. Few clinical trials have investigated the combined effect of counseling on diet and physical activity on PCa patients undergoing RT.

Due to the interest to know the role of the gut microbiota in the immunogenic effect of radiotherapy, there is the need for evidence regarding the most effective approach in promoting a reduction of toxicity and the adoption of a healthy lifestyle in PCa patients.

The results of this innovative project will provide useful information for future interventions and potentially have a large public health impact through the empowerment of patients, who will be able to improve their quality of life, modifying diet and lifestyle.

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9 APPENDICES

9.1 Quality of life: FACT-P (Functional Assessment of Cancer Therapy – Prostate)

Sotto abbiamo elencato delle affermazioni ritenute importanti da persone con la sua stessa malattia.

La preghiamo di indicare in quale misura queste affermazioni riflettono la sua esperienza degli <u>ultimi 7 giorni.</u>

	BENESSERE FISICO	**Per niente**	**Un po'**	**Abba-stanza**	**Molto**	**Moltis-simo**
GP1	Mi manca l'energia	0	1	2	3	4
GP2	Ho nausea	0	1	2	3	4
GP3	Ho difficoltà ad occuparmi delle necessità della mia famiglia a causa delle mie condizioni fisiche	0	1	2	3	4
GP4	Ho dolori	0	1	2	3	4
GP5	Mi danno fastidio gli effetti collaterali della cura	0	1	2	3	4
GP6	Mi sento male	0	1	2	3	4
GP7	Sono costretto a trascorrere del tempo a letto	0	1	2	3	4

	BENESSERE SOCIALE/FAMILIARE	**Per niente**	**Un po'**	**Abba-stanza**	**Molto**	**Moltis-simo**
GS1	Mi sento vicino ai miei amici	0	1	2	3	4
GS2	La mia famiglia mi sostiene moralmente	0	1	2	3	4
GS3	Ho appoggio morale dai miei amici	0	1	2	3	4
GS4	La mia famiglia ha accettato la mia malattia	0	1	2	3	4
GS5	Sono soddisfatto della comunicazione nella mia famiglia a proposito della mia malattia	0	1	2	3	4
GS6	Mi sento vicino al mio compagno/alla mia compagna (o alla persona che mi offre il maggiore appoggio)	0	1	2	3	4
Q1 GS7	*Indipendentemente dalla Sua attività sessuale, La preghiamo di rispondere alla seguente domanda. Se preferisce non rispondere, barri questa casella* ☐ *e passi alla prossima sezione.*					
GS7	Sono soddisfatto della mia attività sessuale	0	1	2	3	4

La preghiamo di indicare in quale misura queste affermazioni riflettono la sua esperienza degli <u>ultimi 7 giorni.</u>

	BENESSERE EMOTIVO	**Per niente**	**Un po'**	**Abba-stanza**	**Molto**	**Moltis-simo**
GE1	Mi sento triste	0	1	2	3	4
GE2	Sono soddisfatto di come sto affrontando la mia malattia	0	1	2	3	4
GE3	Sto perdendo la speranza nella lotta contro la mia malattia	0	1	2	3	4
GE4	Sono nervoso	0	1	2	3	4
GE5	Ho paura al pensiero della morte	0	1	2	3	4
GE6	Ho paura che le mie condizioni possano peggiorare	0	1	2	3	4

	BENESSERE FUNZIONALE	**Per niente**	**Un po'**	**Abba-stanza**	**Molto**	**Moltis-simo**
GF1	Sono in grado di lavorare (si intende anche il lavoro a casa)	0	1	2	3	4
GF2	Il mio lavoro (si intende anche il lavoro a casa) mi gratifica	0	1	2	3	4
GF3	Riesco a godermi la vita	0	1	2	3	4
GF4	Ho accettato la mia malattia	0	1	2	3	4
GF5	Dormo bene	0	1	2	3	4
GF6	Provo ancora piacere nel dedicarmi ad attività di tempo libero	0	1	2	3	4
GF7	Al momento, sono soddisfatto della qualità della mia vita	0	1	2	3	4

La preghiamo di indicare in quale misura queste affermazioni riflettono la sua esperienza degli <u>ultimi 7 giorni.</u>

	ULTERIORI PROBLEMI	**Per niente**	**Un po'**	**Abba-stanza**	**Molto**	**Moltis-simo**
C2	Sto dimagrendo	0	1	2	3	4
C6	Il mio appetito è buono	0	1	2	3	4
P1	Ho dolori e fitte che mi danno disagio	0	1	2	3	4
P2	In certe zone del corpo sento molto dolore	0	1	2	3	4
P3	Il dolore mi impedisce di fare le cose che vorrei	0	1	2	3	4
P4	Sono soddisfatto del mio attuale livello di benessere	0	1	2	3	4
P5	Riesco a sentirmi uomo	0	1	2	3	4
P6	Ho difficoltà ad andare di corpo	0	1	2	3	4
P7	Ho difficoltà ad urinare	0	1	2	3	4
BL2	Urino più frequentemente del solito	0	1	2	3	4
P8	I miei problemi nell'urinare limitano le mie attività	0	1	2	3	4
BL5	Sono in grado di avere e mantenere un'erezione	0	1	2	3	4

9.2 Anxiety assessment: Memorial Anxiety Scale for Prostate Cancer (MAX-PC)

Le Sue sensazioni rispetto al cancro della prostata e al test del PSA.

Vorremmo comprendere meglio come i pazienti affrontano alcuni aspetti del loro trattamento per il cancro della prostata e gli esami frequentemente richiesti durante il loro processo di cura.

I. Qui sotto trova una lista di commenti riportati da uomini in merito al cancro della prostata. Per favore indichi di fianco ad ogni affermazione, con un cerchio intorno al numero, quanto spesso questi commenti sono stati veri per Lei nella settimana passata; per nulla, raramente, qualche volta, spesso.

	Per nulla	Raramente	Qualche volta	Spesso
1. Ogni riferimento al cancro della prostata ha evocato in me sensazioni forti.	0	1	2	3
2. Anche se è una buona idea, trovo che eseguire il test del PSA mi spaventa.	0	1	2	3
3. Ogni volta che ho sentito di un amico o di un personaggio pubblico affetto da cancro della prostata, sono diventato più ansioso rispetto al mio problema di cancro prostatico.	0	1	2	3
4. Quando ho pensato di ripetere il test del PSA, sono diventato più ansioso rispetto al mio problema di cancro prostatico.	0	1	2	3
5. Altre cose mi hanno continuamente fatto pensare al cancro della prostata.	0	1	2	3
6. Mi sono sentito un po' confuso quando ho pensato al cancro della prostata.	0	1	2	3
7. Ho pensato al cancro alla prostata anche se non ne avevo intenzione.	0	1	2	3
8. Ho provato molte sensazioni riguardo al cancro della prostata ma non ho voluto affrontarle.	0	1	2	3
9. Ho avuto più problemi ad addormentarmi perché non riuscivo a togliermi il pensiero del cancro della prostata dalla testa.	0	1	2	3
10. Ho avuto paura che i risultati del test del PSA avrebbero mostrato che la mia malattia stava peggiorando.	0	1	2	3
11. Mi sono spaventato al solo sentire le parole "cancro della prostata".	0	1	2	3

II. Nelle prossime 3 domande per favore indichi quanto frequentemente queste situazioni sono state vere per Lei.

	Per nulla	Raramente	Qualche volta	Spesso
12. Sono stato così in ansia per il mio PSA che ho pensato di rimandarlo.	0	1	2	3
13. Sono stato così preoccupato per il risultato del mio PSA che ho pensato di chiedere al mio dottore di ripeterlo.	0	1	2	3
14. Sono stato così preoccupato per il risultato del mio PSA che ho pensato di ripeterlo in un altro laboratorio per assicurarmi che i risultati fossero accurati.	0	1	2	3

III. Qui sotto trova una serie di affermazioni inerenti alle convinzioni che le persone possono avere sulla propria salute. Pensando alla settimana passata, per favore indichi quanto è in accordo o disaccordo con ciascuna affermazione: completamente d'accordo, d'accordo, in disaccordo, completamente in disaccordo. Per favore indichi la risposta cerchiandola.

	Completamente d'accordo	D'accordo	In disaccordo	Completamente in disaccordo
15. Siccome il cancro è imprevedibile, sento di non poter fare programmi per il futuro.	0	1	2	3
16. La mia paura che il mio cancro peggiori ostacola la possibilità di godermi la vita.	0	1	2	3
17. Ho paura che il mio cancro peggiori.	0	1	2	3
18. Sono più nervoso da quanto mi è stata fatta la diagnosi di cancro.	0	1	2	3

9.3 International Consultation on Incontinence Questionnaire-Short Form

ICIQ - SF

HA PERDITE DI URINA? **Si** ☐ **No** ☐

1) Con quale frequenza le capita di perdere urina?

Mai ☐ Talvolta ☐ Regolarmente ☐ Sempre ☐

2) Secondo la sua personale opinione quanta urina perde comunemente?

Nessuna ☐ Una piccola quantità ☐ Una moderata quantità ☐ Una grande quantità ☐

3) Nel complesso quanto negativamente le perdite influiscono nella sua vita?

0-1 ☐ 2-3 ☐ 4-5 ☐ 6-7 ☐ 8-9 ☐ 10 ☐

In quali circostanze perde urina?

- ☐ Prima di riuscire ad arrivare in bagno
- ☐ Quando tossisco o starnutisco
- ☐ Durante il sonno
- ☐ Durante l'attività fisica
- ☐ Una volta rivestito dopo aver urinato
- ☐ Senza ragioni particolari
- ☐ Sempre

9.4 The revised life orientation test (LOT-R)

LOT_R

Per ciascuna delle affermazioni che seguono, valuti il suo grado di accordo/disaccordo su una scala da (massimo disaccordo) a 5 (massimo accordo) mettendo una crocetta negli appositi spazi. Legg attentamente le affermazioni, e cerchi di rispondere con la massima sincerità, senza lasciarsi influenza dalle sue risposte precedenti, né da quello che reputa sia la valutazione della maggior parte delle person Tenga presente che non ci sono risposte giuste o sbagliate. La ringraziamo per la collaborazione.

Sono fortemente in disaccordo	Sono parzialmente in disaccordo	Non sono né d'accordo né in disaccordo	Sono parzialmente d'accordo	Sono fortemente d'accordo
1	2	3	4	5

AFFERMAZIONI					
1) Nei momenti difficili mi aspetto che tutto vada per il meglio	1	2	3	4	5
2) Mi riesce facile rilassarmi	1	2	3	4	5
3) Se qualcosa può andare per me per il verso sbagliato, sicuramente ci andrà	1	2	3	4	5
4) Sono sempre ottimista riguardo il mio futuro	1	2	3	4	5
5) Traggo molta soddisfazione dallo stare con i miei amici	1	2	3	4	5
6) Per me è importante avere sempre molte cose da fare	1	2	3	4	5
7) Quasi mai mi aspetto che le cose vadano per il meglio	1	2	3	4	5
8) Non mi infastidisco troppo facilmente	1	2	3	4	5
9) Raramente faccio affidamento sulla possibilità che mi possano capitare cose positive	1	2	3	4	5
10) In generale mi aspetto che mi accadranno più cose positive che negative	1	2	3	4	5

9.5 An Italian adaptation of the General Self-Efficacy scale (Sibilia, Schwarzer and Jerusalem 1995)

Pensando a se stesso, indichi quanto è d'accordo con le affermazioni che seguono indicando da 1 a 5 il suo grado di accordo.

Sono fortemente in disaccordo 1	Sono parzialmente in disaccordo 2	Non sono né d'accordo né in disaccordo 3	Sono parzialmente d'accordo 4	Sono fortemente d'accordo 5

1. Riesco sempre a risolvere i problemi difficili se ci provo abbastanza seriamente	1	2	3	4	5
2. Se qualcuno mi contrasta, riesco comunque a trovare il modo o il sistema per ottenere ciò che voglio	1	2	3	4	5
3. Per me è facile attenermi alle mie intenzioni per raggiungere i miei obiettivi	1	2	3	4	5
4. Sono sicuro che potrei affrontare efficacemente eventi inattesi	1	2	3	4	5
5. Grazie alle mie risorse so come gestire situazioni impreviste	1	2	3	4	5
6. Posso risolvere la maggior parte dei problemi se ci metto l'impegno necessario	1	2	3	4	5
7. Rimango calmo nell'affrontare le difficoltà perché posso far conto sulle mie capacità di affrontarle	1	2	3	4	5
8. Quando mi trovo di fronte ad un problema, di solito riesco a trovare parecchie soluzioni	1	2	3	4	5
9. Quando mi piomba addosso qualcosa di nuovo, generalmente sono capace di affrontarlo	1	2	3	4	5
10. Non importa quello che mi può capitare, di solito sono in grado di gestirlo	1	2	3	4	5

9.6 Personal traits questionnaire (ConOR)

Per ciascuna affermazione, indichi quanto in media si riconosce nel comportamento descritto rispetto alla maggior parte delle situazioni/occasioni della sua vita, utilizzando la scala da 0 a 5.

	Per niente	poco	abbastanza	spesso	molto	completamente
1.Ho bisogno che gli altri abbiano una buona opinione di me	0	1	2	3	4	5
2. Mi preoccupa il fatto che gli altri possano essere più bravi di me	0	1	2	3	4	5
3. Se qualcuno mostra improvvisamente un atteggiamento diverso tendo a pensare che ce l'abbia con me	0	1	2	3	4	5
4. Cerco continui consigli e conferme dagli altri per la paura di sbagliare	0	1	2	3	4	5
5. Non sopporto chi fa qualcosa che non rientra nei miei schemi	0	1	2	3	4	5
6. Mi piace comandare	0	1	2	3	4	5
7. Non sempre riesco a dire quello che penso	0	1	2	3	4	5
8. A volte insisto fino a che gli altri perdono la pazienza con me	0	1	2	3	4	5
9. Mi tengo tutto dentro per non dare dispiacere agli altri	0	1	2	3	4	5
10. Mi dedico sempre agli altri	0	1	2	3	4	5
11. Sono sempre a disposizione per gli altri	0	1	2	3	4	5
12. Aiuto gli altri e penso poco a me	0	1	2	3	4	5
13. Se familiari o amici mi chiedono aiuto, metto da parte i miei bisogni per aiutarli	0	1	2	3	4	5
14. Ho sempre pensato che nel soddisfare i bisogni, prima arrivino gli altri e poi arrivo io	0	1	2	3	4	5
15. Quando qualcuno mi chiede qualcosa non riesco a dire di no	0	1	2	3	4	5
16. Ho bisogno di sentirmi utile agli altri	0	1	2	3	4	5
17. Mi piace sapere che gli altri contano su di me	0	1	2	3	4	5

	Per niente	poco	abbastanza	spesso	molto	completamente
18. Quando sono in disaccordo con le persone che mi sono affettivamente vicine, non lo dico	0	1	2	3	4	5
19. Sono controllante nella maggior parte degli ambiti della mia vita	0	1	2	3	4	5
20. Mi piace avere tutto sotto controllo	0	1	2	3	4	5
21. Programmo le mie attività meticolosamente	0	1	2	3	4	5
22. Sono solito fare liste, schemi, piani	0	1	2	3	4	5
23. Tendo generalmente a seguire le mie pianificazioni	0	1	2	3	4	5
24. Devo fare e rifare le cose più volte prima che mi sembrino veramente a posto e ben fatte	0	1	2	3	4	5
25. Ho la tendenza a controllare e ricontrollare le cose più volte del necessario	0	1	2	3	4	5
26. Prima di prendere decisioni rifletto a lungo sui minimi dettagli	0	1	2	3	4	5
27. Lascio che le cose accadano	0	1	2	3	4	5
28. Nell'agire seguo più l'istinto che una pianificazione di quanto va fatto	0	1	2	3	4	5
29. Mi piace decidere all'ultimo momento senza fare programmi	0	1	2	3	4	5
30. Penso che tutti debbano essere un po' egoisti	0	1	2	3	4	5
31. Possiamo essere utili agli altri solo se prima pensiamo a noi stessi	0	1	2	3	4	5
32. Prima degli altri arrivo io	0	1	2	3	4	5
33. Non rinuncerei mai ai miei obiettivi per un'altra persona	0	1	2	3	4	5
34. Tendo a far prevalere gli interessi o le tendenze personali su quelle della collettività	0	1	2	3	4	5

9.7 International Physical Activity Questionnaire (IPAQ)

QUESTIONARIO SULL'ATTIVITA' FISICA

Siamo interessati a conoscere i tipi di attività fisica che le persone fanno come parte della vita quotidiana. Le domande riguarderanno il tempo che lei ha trascorso in attività fisiche negli **ultimi sette giorni**. Cortesemente, risponda ad ogni domanda anche se non si considera essere una persona attiva. Pensi, per favore, alle attività svolte al lavoro, come parte del lavoro svolto in casa ed in giardino, per spostarsi da un luogo all'altro e nel suo tempo libero come divertimento, esercizio fisico o sport.

Pensi a tutte le attività **vigorose**, energiche che ha svolto negli **ultimi sette giorni**. Le attività fisiche vigorose sono quelle che richiedono uno sforzo fisico duro e che la fanno respirare con un ritmo molto più frequente rispetto al normale. Pensi *soltanto* a quelle attività fisiche che lei ha svolto per almeno 10 minuti consecutivamente.

1. Durante gli **ultimi sette giorni**, in quanti giorni lei ha svolto attività fisica vigorosa come sollevare oggetti pesanti, zappare, fare aerobica, o pedalare in bicicletta ad una certa velocità?

_____ **giorni per settimana** ☐ Nessuno (Vada alla domanda 3)

2. Quanto tempo in totale di solito trascorre in attività fisiche **vigorose** in uno di quei giorni?

_____ **ore per giorno** _____ **minuti per giorno** ☐ Non sa / non è sicuro/a

Pensi a tutte quelle attività **moderate** che lei ha svolto negli **ultimi sette giorni**. Le attività moderate sono quelle che richiedono uno sforzo fisico moderato e che la fanno respirare con un ritmo un po' più frequente rispetto al normale. Pensi soltanto a quelle attività fisiche che lei ha svolto per almeno 10 minuti consecutivamente.

3. Durante gli **ultimi sette giorni**, quanti giorni lei ha svolto attività fisica **moderata** come portare pesi leggeri, andare in bicicletta ad un ritmo regolare oppure giocare il doppio a tennis? Non includa il camminare.

_____ **giorni per settimana** ☐ Nessuno (vada alla domanda 5)

4. Quanto tempo in totale di solito trascorre in attività fisiche **moderate** in uno di quei giorni?

_____ **ore per giorno** _____ **minuti per giorno** ☐ Non sa / non è sicuro/a

Pensi al tempo da lei trascorso **camminando negli ultimi sette giorni**. Includa il tempo trascorso sia al lavoro sia a casa, nello spostarsi da un luogo ad un altro e qualsiasi altro cammino che lei ha fatto solo per divertimento, sport, esercizio fisico o per passatempo.

5. Durante gli **ultimi sette giorni**, in quanti giorni lei ha **camminato** per almeno 10 minuti di continuo?

_____ **giorni per settimana** ☐ Nessuno **(Vada alla domanda 7)**

6. Di solito quanto tempo ha trascorso, in uno di quei giorni, **camminando**?

_____ **ore per giorno** _____ **minuti per giorno** ☐ Non sa / non è sicuro/a

L'ultima domanda riguarda il tempo trascorso stando seduto dal lunedì al venerdì negli ultimi sette giorni. Includa il tempo in cui rimane seduto al lavoro, in casa, nello svolgere un corso di formazione, durante il suo tempo libero. Questo può includere il tempo trascorso alla scrivania, nel far visita ad amici, leggendo, 0 seduto/a sdraiato/a per guardare la televisione.

7. Durante gli ultimi sette giorni, in un giorno della settimana, quanto tempo ha trascorso stando seduto?

_____ **ore per giorno** _____ **minuti per giorno** ☐ Non sa / non è sicuro/a

9.8 Self-administered dietary questionnaire

Buongiorno, Vorremmo farle alcune domande sulla sua dieta abituale. Indichi, con una crocetta "X" il numero di porzioni normalmente consumate per i 15 alimenti o gruppi di alimenti elencati nella tabel sottostante.

Si aiuti con le porzioni di riferimento per identificare la sua frequenza di consumo giornaliera, per alimenti elencati dalla domanda n. 1 alla n. 8 e la sua frequenza di consumo settimanale per gli alimer dalla n. 9 alla n. 15.

Se abitualmente consuma una porzione molto piccola o molto grande (rispetto alla porzione di riferiment dimezzi o raddoppi la frequenza di consumo. Per esempio se normalmente beve mezzo litro di vino giorno (corrispondenti a circa 4 bicchieri), la frequenza da segnare in tabella sarà "3-4" porzioni al giorno

E' molto importante che risponda a tutte le domande. Nel caso non consumasse qualche alimento, ricor di fare una crocetta su "mai o raramente".

Con quale frequenza consuma normalmente una porzione dei seguenti alimenti?

ALIMENTI	PORZIONE	FREQUENZA DI CONSUMO AL GIORNO				
		Mai o raramente	Meno di 1 volta /giorno	1 volta /giorno	2 volte /giorno	≥ 3 volte /giorno
1. Pasta o riso di tipo integrale	80 gr	☐	☐	☐	☐	☐
2. Verdura tutti i tipi (sia cruda che cotta)	200 gr (80 gr insalata)	☐	☐	☐	☐	☐
3. Frutta tutti i tipi, anche la spremuta fresca	150 gr	☐	☐	☐	☐	☐
4. Latte e yogurt	1 bicchiere/ vasetto (125 gr)	☐	☐	☐	☐	☐
		Mai o raramente	Meno di 1 volta /giorno	1-2 volte /giorno	3-4 volte /giorno	≥ 5 volte /giorno
5. Pane e fette di tipo integrale	1-2 fette (50 gr)	☐	☐	☐	☐	☐
6. Olio di oliva per cucinare e condire	1 cucchiaio (10 ml)	☐	☐	☐	☐	☐
7. Burro, margarina o panna da cucina per cucinare	1 noce (10 gr)	☐	☐	☐	☐	☐
8. Vino (bianco e rosso)	1 bicchiere (125 ml)	☐	☐	☐	☐	☐
ALIMENTI	**PORZIONE**	**FREQUENZA DI CONSUMO ALLA SETTIMANA**				
		Mai o raramente	Meno di 1 volta /sett	1-3 volte /sett	4-6 volte /sett	≥ 7 volte /sett
9. Carne rossa (bovino, vitello, maiale), affettati e salumi	100 gr (carne) 50 gr (salumi)	☐	☐	☐	☐	☐
10. Carne bianca (pollo, tacchino, coniglio)	100 gr	☐	☐	☐	☐	☐
11. Formaggi freschi e stagionati	100 gr (freschi) 50 gr (stagionati)	☐	☐	☐	☐	☐
12. Bevande dolci o gassate (tipo coca-cola, aranciata, gassosa, ecc)	1 bicchiere (200 ml)	☐	☐	☐	☐	☐
13. Dolci o pasticcini (non fatti in casa), come torte, biscotti, creme o dolci al cucchiaio	100 gr	☐	☐	☐	☐	☐
		Mai o raramente	Meno di 1 volta /sett	1 volta /sett	2-3 volte /sett	≥ 4 volte /sett
14. Pesce (fresco o surgelato) o frutti di mare	150 gr (pesce) 50 gr (frutti di mare)	☐	☐	☐	☐	☐
15. Frutta secca (noci, mandorle, nocciole)	1 pugno (30 gr)	☐	☐	☐	☐	☐
16. Legumi (ceci, lenticchie, piselli, fagioli)	50 gr (secchi) 150 gr (scatola / freschi)	☐	☐	☐	☐	☐

9.9 International Prostate Symptom Score (IPSS)

	Nessuna volta	Meno di una volta su 5	Meno di metà delle volte	Circa metà delle volte	Più di metà delle volte	Quasi sempre
Quante volte nell'ultimo mese ha avvertito un senso di incompleto svuotamento vescicale al temine della minzione?	0	1	2	3	4	5
Nell'ultimo mese quante volte ha urinato meno di due ore dopo l'ultima minzione?	0	1	2	3	4	5
Nell'ultimo mese le è mai capitato di dover urinare in più tempi?	0	1	2	3	4	5
Nell'ultimo mese quante volte ha avuto difficoltà a postporre la minzione?	0	1	2	3	4	5
Nell'ultimo mese quante volte il getto urinario le è parso debole?	0	1	2	3	4	5
Quante volte nell'ultimo mese ha dovuto sforzarsi per iniziare ad urinare?	0	1	2	3	4	5

	Mai	1 volta	2 volte	3 volte	4 volte	5 o più volte
Nel corso dell'ultimo mese quante volte si è alzato di notte per andare ad urinare?	0	1	2	3	4	5

	Bene	Soddisfatto	Abbastanza soddisfatto	cosi cosi	Relativamente insoddisfatto	Male	Molto male
Se dovesse trascorrere il resto della sua vita con la sua condizione urinaria, come si sentirebbe?	0	1	2	3	4	5	6

9.10 Questionnaire on acute and late rectal toxicity

QUESTIONARIO PER IL RILEVAMENTO DELLA TOSSICITA' RETTALE ACUTA E TARDIVA

Le seguenti domande fanno riferimento a quest'ultimo mese.

1. **Quante volte è andato in media di corpo?**
0-1 volte al giorno ☐ 2-4 volte ☐ 4-8 volte ☐ più di 8 volte ☐

2. **Ha avuto diarrea?**
Per nulla ☐ poco ☐ molto ☐ moltissimo ☐

3. **Ha avuto la sensazione di dover andare subito di corpo senza emettere feci?**
Mai ☐ a volte ☐ spesso ☐ di continuo ☐

4. **Ha avuto uno stimolo imperioso ad andare di corpo?**
Mai ☐ a volte ☐ spesso ☐ di continuo ☐

5. **Ha perso involontariamente feci?**
Mai ☐ a volte ☐ spesso ☐ tutti i giorni ☐

6. **Ha avuto perdite di muco dal retto?**
Per nulla ☐ poco ☐ molto ☐ moltissimo ☐

7. **Ha dovuto usare assorbenti per perdita di muco o feci?**
Mai ☐ fino a 2 volte la sett. ☐ più di 2 volte la sett. ☐ tutti i giorni ☐

8. **Ha avuto dolore a livello del retto?**
Per nulla ☐ poco ☐ molto ☐ moltissimo ☐

9. **Ha notato sangue nelle feci?**
Mai ☐ fino a 2 volte la sett. ☐ più di 2 volte la sett. ☐ tutti i giorni ☐

10. **Ha assunto dei farmaci per i disturbi su menzionati?**
Mai ☐ fino a 2 volte la sett. ☐ più di 2 volte la sett. ☐ tutti i giorni ☐
Quali farmaci? _____

11. **Ha usato farmaci a livello del retto? (perette, pomate…)**
Mai ☐ fino a 2 volte la sett. ☐ più di 2 volte la sett. ☐ tutti i giorni ☐
Quali farmaci? _____

Le seguenti domande fanno riferimento **agli ultimi 6 mesi (da non compilare in questionario basale e fine RT)**.

12. **Ha dovuto fare delle trasfusioni di sangue per perdite di sangue dal retto?**
Mai ☐ 1 o 2 ☐ più di 2 ☐

13. **Ha dovuto eseguire trattamenti con laser mediante rettoscopia?**
Mai ☐ 1 o 2 ☐ più di 2 ☐

14. **Ha eseguito ossigenoterapia iperbarica?**
No ☐ si ☐

15. **Per i disturbi su riportati, ha dovuto subire operazioni chirurgiche?**
No ☐ si ☐
Quale operazione? _____

9.11 International index of Erectile Function – IIEF

QUESTIONARIO DELLA FUNZIONE ERETTILE

Sezione 1. Attività sessuale.

Queste domande si riferiscono alla sua attività sessuale nelle ultime 4 settimane. la preghiamo di rispondere ad ogni domanda segnando una sola casella con una barra. Se non è sicuro sulla risposta da dare la preghiamo di scegliere quella che ritiene migliore.

Nel rispondere a queste domande vanno tenute presenti le seguenti definizioni:

- **Rapporto sessuale**: viene definito come la penetrazione (introduzione del pene) vaginale della partner
- **Attività sessuale**: Include rapporti sessuali, accarezzamenti, preliminari e masturbazione
- **Eiaculazione**: viene definita come l'emissione dello sperma dal pene (o la sensazione che ciò avvenga)
- **Stimolazione sessuale**: include situazioni come giochi erotici con una partner, guardare immagini erotiche ecc.

1. Nelle ultime 4 settimane, quanto spesso è stato in grado di avere una erezione ducante l'attività sessuale?

- Non ho avuto nessuna attività sessuale 0 ☐
- Quasi sempre o sempre 5 ☐
- La maggior parte delle volte (molto più della metà delle volte) 4 ☐
- Qualche volta (circa la metà delle volte) 3 ☐
- Poche volte (molto meno della metà delle volte) 2 ☐
- Quasi mai o mai 1 ☐

2. Nelle ultime 4 settimane, quando ha avuto delle erezioni in seguito a stimolazione sessuale, quanto spesso queste erezioni erano tali da permettere la penetrazione ?

- Non ho avuto nessuna attività sessuale 0 ☐
- Quasi sempre o sempre 5 ☐
- La maggior parte delle volte (molto più della metà delle volte) 4 ☐
- Qualche volta (circa la metà delle volte) 3 ☐
- Poche volte (molto meno della metà delle volte) 2 ☐
- Quasi mai o mai 1 ☐

Le prossime tre domande riguardano le erezioni che Lei può aver avuto durante il rapporto sessuale

3. Nelle ultime 4 settimane, quando ha tentato di avere un rapporto sessuale, quanto spesso è stato in grado di penetrare la Sua partner ?

- Non ho avuto nessuna attività sessuale 0 ☐
- Quasi sempre o sempre 5 ☐
- La maggior parte delle volte (molto più della metà delle volte) 4 ☐
- Qualche volta (circa la metà delle volte) 3 ☐
- Poche volte (molto meno della metà delle volte) 2 ☐
- Quasi mai o mai 1 ☐

4. Nelle ultime 4 settimane, durante il rapporto sessuale quanto spesso è stato in grado di mantenere l'erezione dopo aver penetrato la partner ?

- Non ho avuto nessuna attività sessuale 0 ☐
- Quasi sempre o sempre 5 ☐
- La maggior parte delle volte (molto più della metà delle volte) 4 ☐
- Qualche volta (circa la metà delle volte) 3 ☐
- Poche volte (molto meno della metà delle volte) 2 ☐
- Quasi mai o mai 1 ☐

5. Nelle ultime 4 settimane, durante il rapporto sessuale quanto difficile è stato mantenere la sua erezione fino al completamento del rapporto ?

- Non ho tentato di avere rapporti sessuali 0 ☐
- Estremamente difficile 1 ☐
- Molto difficile 2 ☐
- Difficile 3 ☐
- Poco difficile 4 ☐
- Per niente difficile 5 ☐

6. Nelle ultime 4 settimane, quante volte ha tentato di avere rapporti sessuali ?

- Non ho tentato di avere rapporti sessuali 0 ☐
- 1-2 tentativi 1 ☐
- 3-4 tentativi) 2 ☐
- 5-6 tentativi 3 ☐
- 7-10 tentativi 4 ☐
- Più di 11 tentativi 5 ☐

7. Nelle ultime 4 settimane, quando ha tentato di avere un rapporto sessuale, quanto spesso è stato soddisfacente per lei personalmente ?

- Non ho avuto nessuna attività sessuale 0 ☐
- Quasi sempre o sempre 5 ☐
- La maggior parte delle volte (molto più della metà delle volte) 4 ☐
- Qualche volta (circa la metà delle volte) 3 ☐
- Poche volte (molto meno della metà delle volte) 2 ☐
- Quasi mai o mai 1 ☐

8. Nelle ultime 4 settimane, quanto piacevoli sono stati per lei i suoi rapporti sessuali ?

- Non ho tentato di avere rapporti sessuali 0 ☐
- Estremamente piacevoli 5 ☐
- Molto piacevoli 4 ☐
- Abbastanza piacevoli 3 ☐
- Non molto piacevoli 2 ☐
- Per niente piacevoli 1 ☐

9. Nelle ultime 4 settimane, quando ha avuto una stimolazione sessuale oppure un rapporto sessuale, quanto spesso ha eiaculato ?

- Non ho avuto nessuna attività sessuale 0 ☐
- Quasi sempre o sempre 5 ☐
- La maggior parte delle volte (molto più della metà delle volte) 4 ☐
- Qualche volta (circa la metà delle volte) 3 ☐
- Poche volte (molto meno della metà delle volte) 2 ☐
- Quasi mai o mai 1 ☐

10. Nelle ultime 4 settimane, quando ha avuto una stimolazione sessuale oppure un rapporto sessuale, quanto spesso ha provato la sensazione di orgasmo con o senza eiaculazione ?

- Non ho avuto nessuna attività sessuale 0 ☐
- Quasi sempre o sempre 5 ☐
- La maggior parte delle volte (molto più della metà delle volte) 4 ☐
- Qualche volta (circa la metà delle volte) 3 ☐
- Poche volte (molto meno della metà delle volte) 2 ☐
- Quasi mai o mai 1 ☐

Le prossime due domande riguardano il desiderio sessuale. Si definisce desiderio sessuale una sensazione che include la voglia di avere un'esperienza sessuale (es. masturbazione o rapporto sessuale), il pensare al sesso, od il sentirsi frustrati per la mancanza di attività sessuale.

11. Nelle ultime 4 settimane, quanto spesso ha provato desiderio sessuale ?

- Quasi sempre o sempre 5 ☐
- Spesso (molto più della metà delle volte) 4 ☐
- Qualche volta (circa la metà delle volte) 3 ☐
- Poche volte (molto meno della metà delle volte) 2 ☐
- Quasi mai o mai 1 ☐

12. Come valuterebbe il suo livello di desiderio sessuale relativo alle ultime quattro settimane?

- Molto alto 5 ☐
- Alto 4 ☐
- Moderato 3 ☐
- Basso 2 ☐
- Molto basso o del tutto nullo 1 ☐

13. Nelle ultime quattro settimane in che misura è stato soddisfatto dalla sua vita sessuale complessiva ?

- Molto soddisfatto 5 ☐
- Moderatamente soddisfatto 4 ☐
- Più o meno ugualmente soddisfatto ed insoddisfatto 3 ☐
- Moderatamente insoddisfatto 2 ☐
- Molto insoddisfatto 1 ☐

14. Nelle ultime quattro settimane, in che misura è stato soddisfatto della sua relazione sessuale con la partner ?

- Molto soddisfatto 5 ☐
- Moderatamente soddisfatto 4 ☐
- Più o meno ugualmente soddisfatto ed insoddisfatto 3 ☐
- Moderatamente insoddisfatto 2 ☐
- Molto insoddisfatto 1 ☐

15. Nelle ultime quattro settimane, come valuterebbe il suo livello di fiducia nel poter raggiungere e mantenere una erezione ?

- Molto alto 5 ☐
- Alto 4 ☐
- Moderato 3 ☐
- Basso 2 ☐
- Molto basso 1 ☐

9.12 Informed Consent Forms and Consent for processing of personal data (privacy disclosure)

Microstyle

STUDIO DI INTERVENTO SU STILE DI VITA E MICROBIOTA IN PAZIENTI SOTTOPOSTI A RADIOTERAPIA PER TUMORE ALLA PROSTATA

1442

FOGLIO INFORMATIVO E MODULO DI CONSENSO INFORMATO

PREMESSA

Questo foglio ha lo scopo di fornirLe informazioni, e di chiedere il Suo consenso in merito ad una Sua partecipazione ad un progetto di ricerca, che si svolge presso l'Istituto Europeo di Oncologia.

La Sua scelta di partecipare è del tutto libera, Le sarà dato il tempo necessario per leggere attentamente questo documento che riporta le informazioni forniteLe a voce dal medico responsabile del progetto o suo delegato e Le è data la possibilità, se lo desidera, di discuterne con persone di Sua fiducia, oppure con il Suo medico di medicina generale.

Qualora riscontrasse aspetti non del tutto chiari o ritenesse utili ulteriori informazioni, la invitiamo a discuterli con la persona responsabile del progetto.

Non sottoscriva il consenso informato se non è sicuro di aver compreso fino in fondo le informazioni riportate in questo documento.

Se deciderà di partecipare a questo progetto Le verrà consegnata una copia del presente documento, firmato e datato.

Qualora decidesse di non partecipare al progetto Le sarà comunque garantita la stessa attenzione che Le è stata riservata fino ad oggi.

TITOLO DEL PROGETTO:

Studio di intervento su stile di vita e microbiota in pazienti sottoposti a radioterapia per tumore alla prostata – Studio MicroStyle

RAZIONALE E OBIETTIVO DEL PROGETTO:

La radioterapia è l'approccio non chirurgico standard al trattamento del tumore della prostata, ma può provocare alcuni effetti collaterali a carico dell'apparato gastrointestinale e genito-urinario che possono influire in modo significativo sulla qualità della vita.

L'obiettivo di questo studio è di valutare l'effetto di un intervento di 6 mesi mirato al miglioramento dello stile di vita in un gruppo di uomini trattati per tumore alla prostata utilizzando anche un dispositivo contapassi. Questa sperimentazione è innovativa perché propone un intervento di consulenza nutrizionale e fisioterapica per migliorare la qualità di vita, controllare gli effetti collaterali della radioterapia e promuovere comportamenti salutari.

Le feci e il sangue contengono informazioni importanti sullo stato del sistema gastrointestinale e del sistema immunitario. Le raccoglieremo per studiare come il cambiamento dell'alimentazione e lo stile di vita durante la radioterapia influenzerà le comunità di batteri del nostro intestino (microbioma), il sistema immunitario e la risposta alla radioterapia, e come queste condizioneranno a loro volta la qualità di vita.

A CHI È RIVOLTO:

Lo studio è rivolto a uomini canditati alla radioterapia per tumore alla prostata. I partecipanti tra i pazienti afferenti al Dipartimento di Radioterapia del nostro Istituto saranno invitati ad aderire allo studio.

COSA COMPORTA LA PARTECIPAZIONE A QUESTO PROGETTO:

I partecipanti allo studio saranno reclutati tra gli uomini sottoposti a radioterapia in due centri (IEO, Milano e INT Fondazione Pascale, Napoli). Prevediamo di arruolare un totale di 300 pazienti e dividerli casualmente in due gruppi: gruppo di intervento (GI) e gruppo di controllo (GC). I partecipanti assegnati al GI incontreranno un dietista e un fisioterapista, prima della radioterapia, per ricevere raccomandazioni personalizzate sulla dieta e sull'esercizio fisico, in base al loro stato di salute, per migliorare lo stile di vita generale e ridurre gli effetti collaterali della radioterapia (problemi intestinali e/o urinari). Inoltre il dietista darà indicazioni per limitare gli effetti collaterali gastrointestinali riducendo il consumo di alcuni alimenti, e il fisioterapista fisserà obiettivi individualizzati in base alle capacità, allo stile di vita e alle preferenze per aumentare l'attività fisica e ridurre la sedentarietà. Inoltre il fisioterapista fornirà delle indicazioni per favorire l'allenamento muscolare del pavimento pelvico per migliorare la salute genito-urinaria, riducendo l'incontinenza urinaria che può seguire i trattamenti alla prostata, l'eventuale disfunzione erettile e il dolore pelvico dovuto agli spasmi muscolari. A tutti i partecipanti verrà fornito un dispositivo contapassi, al fine di monitorare e interferire con l'attività fisica e il livello di sedentarietà. Nel corso dell'intervento raccoglieremo alcune misure (altezza, peso e composizione corporea).

I partecipanti inclusi nel GC riceveranno all'inizio dello studio dei consigli generali per i pazienti sottoposti alla radioterapia e solo successivamente, dopo i primi 6 mesi, questo gruppo passerà all'intervento come proposto per il GI e sarà seguito per ulteriori 6 mesi.

Sono previste almeno 4 visite, 3 prelievi di sangue e 4 prelievi di feci nel corso dello studio. Inoltre ad ogni visita verrà invitato a compilare alcuni questionari:

- un questionario sulla qualità della vita, costituito da una serie di domande che valutano lo stato di benessere generale, emotivo e altre domande legate alla sintomatologia gastrointestinale e genito-urinale.
- due questionari che valutano eventuali problemi urinari e di incontinenza;
- un questionario alimentare che indaga i consumi dei principali gruppi alimentari nel mese precedente la compilazione;
- alcuni questionari che valutano il livello di ansia legata ai trattamenti per il tumore alla prostata, la personalità e l'attitudine ad affrontare le cure;
- un questionario per la misurazione del livello di attività fisica eseguita durante il tempo libero nei 7 giorni precedenti.

RISCHI E DISAGI

Non vi sono rischi aggiuntivi per i soggetti ai quali sono offerte le migliori condizioni di assistenza clinica, rispetto alla normale pratica standard.

VANTAGGI E SVANTAGGI

Nessun vantaggio/svantaggio per il paziente che aderisce allo studio. I risultati di questo studio potranno contribuire ad una migliore comprensione dell'interazione tra stile di vita, microbioma intestinale e biomarcatori sierici sugli effetti collaterali della radioterapia. Questi risultati saranno senz'altro utili in futuro per la definizione di raccomandazioni per soggetti a rischio e lo sviluppo di interventi mirati.

COSTI E COMPENSI CORRELATI AL PROGETTO

Non sono previsti costi legati alla partecipazione al progetto e nemmeno compensi o rimborsi di spese.

ASSICURAZIONE

La copertura assicurativa dello studio rientra nella polizza Responsabilità Civile N° C/209443874 attiva presso l'Istituto Europeo di Oncologia, che opera nei seguenti termini:

Periodo di copertura:
Massimale aggregato 15.000.000 per intero periodo di copertura;
Sottolimite di 10.000.000 per sinistro/persona o sinistro in serie.

In caso di danno connesso con la sperimentazione a cui lei partecipa, dovrà darcene immediata comunicazione. In questo caso, Lei autorizza la compagnia d'assicurazioni a prendere visione delle informazioni sulla sua anamnesi e di tutte le informazioni relative al Suo stato di salute collegate al danno subito.

RISERVATEZZA

Le cartelle cliniche dei pazienti sono strettamente confidenziali nei limiti garantiti dalla legge (D. Lgs: 196/03) e tali rimarranno durante la Sua partecipazione allo studio ed al termine di esso. I dati raccolti durante lo studio saranno analizzati da programmi computerizzati e verranno conservati per più di 15 anni. Lei è libera/o di ritirarsi dallo studio in qualunque momento. In quel caso noi vorremmo continuare a conservare i Suoi dati, e con il Suo consenso, vorremmo continuare a raccogliere le informazioni sul Suo stato di salute anche in futuro. Nel caso in cui Lei desiderasse di ritirarsi dallo studio e non permettesse che le informazioni che la riguardano siano conservate, i dati già presenti in archivio verranno resi anonimi (cioè non sarà possibile in alcun modo collegarli a Lei) e non saranno più raccolti altri dati. In tal caso dovrà comunicarlo per iscritto tramite il Suo medico all'Istituto Europeo di Oncologia. I dati verranno analizzati esclusivamente a scopo di ricerca ed in alcun modo il suo nome o altri elementi che possano identificarla saranno utilizzati nelle pubblicazioni scientifiche relative a questo studio.

PARTECIPAZIONE VOLONTARIA /DIRITTO DI RIFIUTARE O DI RITIRARSI

Lei può scegliere liberamente di partecipare o meno allo studio, dopo essere stato/a adeguatamente informato/a dal medico sugli scopi e le procedure dello studio di ricerca e sulle opzioni alternative. Se Lei deciderà di partecipare allo studio, sarà libero/a di ritirarsi in qualunque momento. Se dovesse decidere di ritirarsi Le chiediamo di parlarne prima con il Suo medico. In questo caso Le chiediamo di contattarci periodicamente o tramite il suo medico curante per un aggiornamento sulla sua situazione clinica.

NUOVE INFORMAZIONI DERIVANTI DA QUESTO E DA ALTRI STUDI

Lei ha diritto ad essere informato degli sviluppi del presente studio clinico e dei suoi risultati finali. Ha inoltre il diritto di essere informato di tutti gli ulteriori risultati ottenuti da altri studi, che potrebbero essere importanti per il Suo trattamento oppure influire sulla Sua disponibilità a proseguire.

PERSONE DA CONTATTARE

In caso di necessità può contattare il medico incaricato del presente studio la Dott.ssa Giulia Marvaso (e-mail giulia.marvaso@ieo.it) Tel 02 94372696. In alternativa potrà contattare la Dr.ssa Patrizia Gnagnarella (e-mail: patrizia.gnagnarella@ieo.it), oppure è possibile chiamare presso la linea telefonica: Tel. 02 57489823

Potrà contattarci qualora desideri ulteriori informazioni su questo studio prima di decidere se parteciparvi o meno, o in qualsiasi altro momento. È inoltre la persona da chiamare nell'eventualità in cui, avendo Lei deciso di partecipare, si manifestino gravi effetti collaterali del trattamento.

MODULO DI CONSENSO INFORMATO

MicroStyle

STUDIO DI INTERVENTO SU STILE DI VITA E MICROBIOTA IN PAZIENTI SOTTOPOSTI A RADIOTERAPIA PER TUMORE ALLA PROSTATA

DICHIARAZIONE DEL MEDICO CHE OTTIENE IL CONSENSO INFORMATO

Ho spiegato interamente in che cosa consiste questo studio clinico al paziente _____
_____.

A giudizio mio e del paziente, vi è stato sufficiente accesso all'informazione, inclusa quella relativa a rischi e benefici, per poter formulare una decisione informata.

DATA: _____

FIRMA DEL MEDICO: _____

NOME DEL MEDICO: _____

DICHIARAZIONE DELLA PAZIENTE

Ho preso visione del modulo di consenso informato predisposto dall'Istituto Europeo di Oncologia, confermo che mi è stata offerta sufficiente opportunità di discutere di ogni aspetto dello studio con il medico responsabile, il quale si è reso disponibile per ogni ulteriore informazione riguardante lo studio stesso Ho compreso che la mia partecipazione è volontaria. Sono stato/a sufficientemente informato/a riguardo agli scopi ed ai metodi della sperimentazione e sono in grado di decidere la mia libera e volontaria partecipazione a questo studio. Ho compreso che posso liberamente decidere di interrompere la mia partecipazione allo studio in qualunque momento.
Ho ricevuto copia del modulo di consenso informato.

FIRMA DEL PAZIENTE: _____ Data:_____

NOME DEL PAZIENTE (in stampatello):_____

Data di nascita del paziente: _____

FIRMA DEL TESTIMONE IMPARZIALE_____ Data_____

NOME E COGNOME DEL TESTIMONE IMPARZIALE

(in stampatello)_____

(richiesta solo se il paziente o il suo rappresentante legalmente riconosciuto non sono in grado di leggere – DM N°162 del 15.7.97 art. 4.8.9)

FIRMA DEL RICERCATORE: _____

Data _____

NOME DEL RICERCATORE (in stampatello):_____

Numero di registrazione del paziente _____

Informativa ai sensi dell'art.13 del Regolamento Generale sulla Protezione dei Dati Personali (Regolamento UE 2016/679)

Gentile Signore,
ad integrazione di tutte le spiegazioni che lo sono state fornite dai professionisti sanitari per illustrarle, dal punto di vista clinico-scientifico: obiettivi, modalità, eventuali rischi e benefici della ricerca per la quale è stata proposta la sua partecipazione; con la presente intendiamo informarla in modo specifico sugli aspetti inerenti l'utilizzo dei suoi dati personali* ed in particolare delle informazioni sul suo stato di salute** che derivano dalla sua partecipazione al progetto di ricerca.

L'Istituto Europeo di Oncologia è un Istituto e Cura a Carattere Scientifico, per il quale la ricerca è parte integrante della sua missione. Tutte le ricerche sono controllate e approvate dal Comitato Etico, e prevedono alla luce dell'attuale normativa vigente, il suo consenso specifico al trattamento per il trattamento dei suoi dati personali.

I dati personali saranno trattati su supporto informatico e/o cartaceo da personale appositamente autorizzato nel rispetto della normativa vigente in materia di protezione dei dati **personali**. Qualora dovesse essere necessario il coinvolgimento di società o professionisti esterni, ciò avverrà solo previo accordo specifico con clausole di salvaguardia per i suoi diritti in materia di protezione dei dati personali (nomina a Responsabili del Trattamento). Qualora il coinvolgimento di terzi nel progetto di ricerca comporti anche un trasferimento dei suoi dati personali all'estero; in caso di paesi appartenenti all'Unione Europea, come previsto dalla normativa vigente, valgono gli stessi principi, le stesse regole, diritti e tutele presenti in Italia; in casi di paesi non appartenenti all'Unione Europea, il trasferimento potrà avvenire esclusivamente nel rispetto di clausole contrattuali mediante le quali viene richiesto di garantire gli stessi standard di sicurezza e tutela europei.

I risultati della ricerca potranno essere divulgati in modo aggregato ai dati di altri pazienti (senza che sia possibile risalire a lei), in pubblicazioni scientifiche e/o presentati nel corso di convegni, congressi, eventi scientifici-divulgativi in genere.

I suoi dati personali saranno conservati per il tempo necessario: a completare lo studio; a redigere rapporti sullo studio o presentazioni scientifiche; e per ricerche future, fino ad un massimo di 30 anni.
Non è previsto nessun compenso, ora e in futuro, a fronte della suddetta prestazione e dei diritti di utilizzo concessivi.
Titolare del trattamento è il l'Istituto Europeo di Oncologia con sede legale in via Filodrammatici 10, 20121 Milano, e con sede operativa principale in Via Ripamonti n. 435, 20141 Milano.
Per esercitare i suoi diritti in tema di accesso, rettifica, cancellazione, limitazione, conservazione, opposizione, portabilità dei dati personali; per conoscere la denominazione delle società o soggetti terzi che tratteranno i suoi dati personali, o per conoscere il suo diritto di reclamo ad una autorità di controllo, può rivolgersi direttamente al **Responsabile Protezione Dati Personali,** utilizzando i seguenti dati di contatto:

- **Indirizzo** Via Giuseppe Ripamonti n° 435, 20141 Milano
- **Tel** 02.57489285
- **Mail** privacy@ieo.it / direzione.sanitaria@ieo.it
- **PEC** direzionesanitariaieo@pec.it

** **Dato personale**: qualunque informazione riguardante una persona fisica identificata o identificabile "interessato"; si considera identificabile la persona fisica che può essere identificata, direttamente o indirettamente, con particolare riferimento a un identificativo come il nome, un numero di identificazione, dati relativi all'ubicazione, un identificativo on line o a uno o più elementi caratteristici della sua identità fisica, fisiologica, genetica, psichica, economica, culturale o sociale (art. 4, comma 1, Regolamento UE 2016/679).*

*** **Dato relativo alla salute**: dati personali attinenti alla salute fisica o mentale di una persona fisica, compresa la prestazione di servizi di assistenza sanitaria, che rivelano informazioni relative al suo stato di salute (art. 4, comma 15, Regolamento UE 2016/679).*

Consenso

Io sottoscritta/o .....
nata/o in data: ____/____/_____ ricevuta l'informativa ai sensi dell'art.13 del Reg. Ue 2016/679, **acconsento** al trattamento dei miei dati personali secondo le modalità e per le finalità indicate.

Milano, _____/_____/_____ Firma.....