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## Radiation Therapy Strategies in Geriatric Patients: A Literature Review

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### Abstract

For humans, aging is defined as a universal biological process that manifests itself as a decrease in functional capacity and an increase in the risk of morbidity and mortality over time. Age is considered the single most significant risk factor for many chronic conditions including malignancies. The incidence of breast, lungs, prostate, colorectal, stomach, thyroid, pancreas, and ovarian cancers, as well as several types of leukemia, increase exponentially with age. Oncologists are often faced with difficulties when treating this population. Even though elderly and younger individuals seem to be able to get the same benefits to result from treatment, the elderly are at a greater risk of experiencing toxicity, serious side effects and death. A comprehensive multidisciplinary evaluation in elderly individuals with cancer can identify the risks and benefits of toxicity due to treatment plans including morbidity and mortality. Radiotherapy can be the solution in the elderly with cancer, especially in patients at high risk for systemic therapy or surgery. Radiotherapy with modern techniques and fractionation adjustments (hypofractionation) can minimize the toxicity due to therapy and can be well tolerated by elderly individuals with cancer.

**Keywords:** aging, cancer, radiotherapy, toxicity, functional status

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## Introduction

Aging is not a disease but, aging is the main risk factor for so many chronic diseases. The medical discipline that focused with all aspects of the phenomena of aging including health and disease in the elderly is called Gerontology. On the other hand, geriatrics is defined as the branch of medicine that focused on the problems and diseases of the elderly.<sup>1</sup> As the increasing proportion of the elderly, it is important to have a better understanding of the complexity of older people's health care and needs. Based on An Aging World's report, people aged >65 years accounted for 8,5% of the world's total population in 2015. This number is projected to increase by 12% and 16.7% in 2030 and 2050.<sup>2</sup>

The demographic transition that occurred in Indonesia has a significant impact on the age shift of the population. The suppressed population growth rate,

added by improvements in life expectancy, resulted in a relatively low birth rate and an increased elderly population. Globally, Indonesia is placed in the eighth position on the most elderly populated country in the world. There was 18.1 million elderly in 2010 and 25.64 million (9.6% of all population) in 2019.<sup>3,4</sup> This phenomenon showed that Indonesia is transitioning towards a country with an aging population.<sup>4</sup>

The majority of patients with cancer are older and elderly adults. The addition of chronological age becomes one of the risk factors for cancer. 60% of newly diagnosed malignancies and 70% of all cancer deaths occur in individuals over 65.<sup>5</sup> Berger et al. reported that the incidence and mortality rate of cancer increased 10 and 16 times respectively in individuals over 65 years old compared to younger people. Prostate, bladder, colon, uterine, pancreatic, stomach,

rectal, and lung cancers are the leading cause of cancer-related deaths among patients 65 years and older.<sup>5</sup>

Radiotherapy (RT) is one of the critical modalities in cancer management. More than 50% of cancer patients will require RT as part of cancer management.<sup>6</sup> RT can be used as definitive, palliative, or adjuvant treatment together with other therapeutic modalities, such as surgery and systemic therapy. In the elderly, where surgery and chemotherapy might result in worse quality of life (QoL), RT can be an effective and optimal treatment option.<sup>7</sup> Nevertheless, elderly patients are more often treated with non-curative or palliative intent RT.<sup>8</sup>

This opinion was strengthened by the data from the Department of Radiation Oncology Dr. Cipto Mangunkusumo Hospital (unpublished data). **Figure 1** showed that there was an increasing number of elderly patients aged  $\geq 60$  years (elderly criteria based on Law Number 13 of 1998) treated by RT during 2008 – 2019 (**Figure 1**). As the result, the multidisciplinary integration of oncology and geriatrics into one individualized treatment plan is essential to optimize the therapeutic outcomes for elderly patients with cancer.

### Characteristics of Elderly Patients

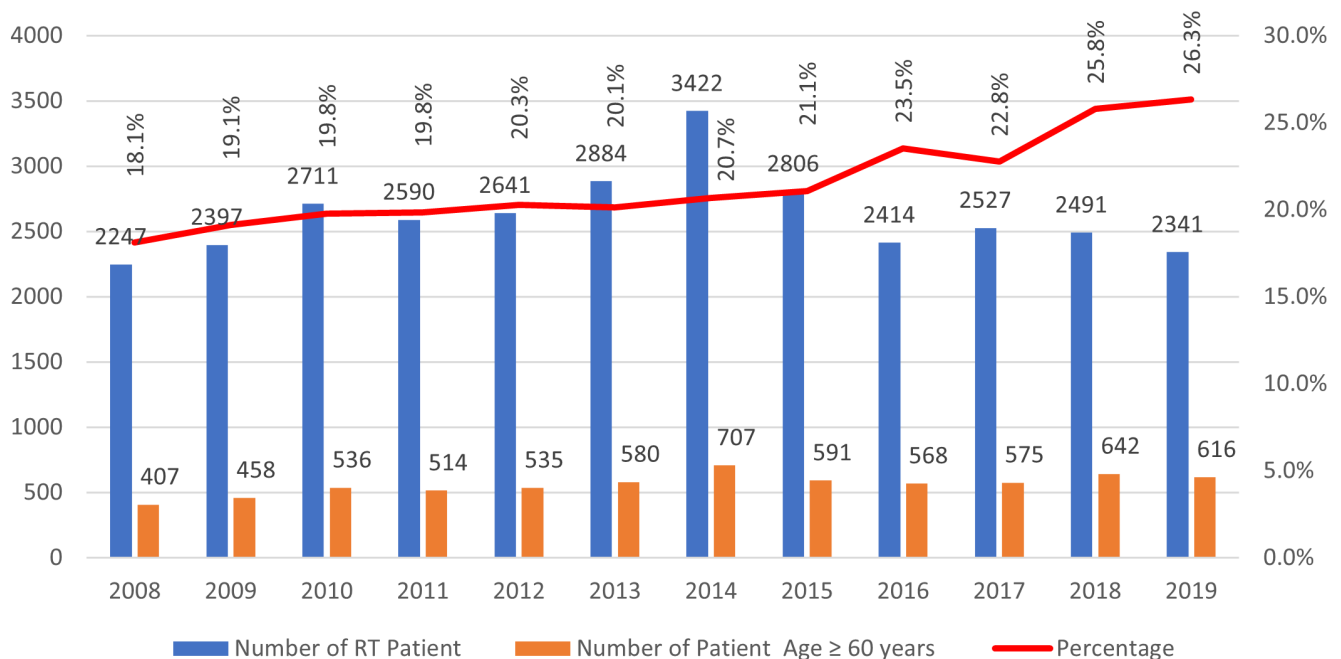
Age-related changes have been identified and occurred in all cells, tissues, organs, and systems of the body. One of the most significant characteristics of aging is the failure to maintain homeostasis under physiological stress conditions. Aging is not merely a progressive functional decrease. However, it produces anatomical

and physiological changes that can lead to decompensation of the relevant systems when the body is exposed to stimuli that exceed the threshold. The loss of response adaptability is ultimately associated with an increase in vulnerability, which results in a decrease in the health status of the elderly.<sup>9</sup>

Anatomical and physiological changes significantly affect systems and organs, such as the cardiovascular system, lungs, liver, gastrointestinal tract, kidneys, central nervous, and musculoskeletal system. These changes will form a domino effect on other major organ systems. Decreased function of the digestive system, liver, and kidneys will significantly impact changes in pharmacokinetics and pharmacodynamics of a drug.<sup>9,10</sup> These changes significantly affect the management of the elderly with cancer, especially the risk of increased toxicity and changes in therapeutic doses that directly affect the response to therapy.<sup>10</sup>

The second characteristic is a decrease in functional status. Functional status is one indicator of individual independence in carrying out daily activities. Measurement of functional status is often also associated with the quality of life of the elderly.<sup>11</sup> A decrease in functional status will cause the elderly to be in a state of immobilization, which results in dependence on others.<sup>12</sup> Assessment of functional status in adults with cancer generally uses the Eastern Cooperative Oncology Group (ECOG) or Karnofsky Performance Status scales (KPS) instruments.

The third characteristic is comorbidity and multimorbidity in the elderly. Comorbidity and multimorbidity are strongly associated with a more



**Figure 1.** Number and Percentage of Patients Age  $\geq 60$  years in the Department of Radiation Oncology, Dr. Cipto Mangunkusumo Hospital (2008 – 2019)

impoverished life in the elderly with cancer. Common comorbidities in the elderly, such as cardiovascular disease, diabetes, and chronic renal insufficiency, can increase the risk of complications related to cancer treatment.<sup>10,13</sup> The incidence of comorbidities increases with age. In Indonesia, based on the results of the 2007 Riskesdas follow-up analysis by the Ministry of Health, only 15% of the elderly are healthy, 34.6% suffer from one type of disease, and 50.4% suffer from two or more types of disease (multimorbidity).<sup>14</sup>

The fourth characteristic is malnutrition. Malnutrition is a term that represents any condition caused by insufficient, excessive, or unbalanced consumption, absorption, or utilization of nutrients. As the severity and duration of malnutrition increase, malnutrition can lead to decreased health status, including a decrease in physical and cognitive function, loss of vitality, and decreased overall quality of life. With increasing age, appetite, and food intake may decrease, even without accompanying acute or chronic disease. Weight loss is the primary manifestation of malnutrition in the elderly. Detection of weight loss is vital in the care of elderly individuals. This is because a decrease in body weight shows the degree and progression of malnutrition and indicates an unfavorable prognosis.<sup>15</sup>

### **Theory of the Correlation between Aging and Cancer**

Breast cancer, lung, prostate, colorectal, stomach, thyroid, pancreas, and ovaries, as well as some types of leukemia, increase exponentially with age. As previously described, older patients experience many age-related biological changes, multimorbidity, and the impact of pharmacological and non-pharmacological therapies, as well as the influence of lifestyle, environmental and psychosocial factors, all of which affect decreasing physiological reserves and increased risk of vulnerability.<sup>16</sup>

Cancer and aging can be considered as two sides of the same cellular and molecular process. Accumulation of cell mutation is the leading theory for the aging mechanism.<sup>17</sup> It is believed to also play an essential role in the pathogenesis of many malignancies, such as supporting carcinogenesis, promoting tumor cell development, and causing resistance to cancer therapy.<sup>16</sup>

The inflammatory process can serve as an acute response of the immune system to dangerous conditions, such as traumatic tissue injury or pathogenic infection. However, the acute inflammatory response at the molecular level may be impaired in elderly individuals, leading to an increased

vulnerability to infection. In the elderly, many tissues may be in a state of chronic inflammation, even without signs of infection. In chronic inflammation, there are many features of acute inflammation, but they are usually low-grade, persistent, and accumulated, producing a response that leads to tissue degeneration and even maladaptation.<sup>18</sup> In cancer, substantial evidence suggests that chronic inflammatory processes increase cancer risk. Chronic inflammation triggers carcinogenesis, such as precipitating genetic mutations or through mechanisms of epigenetic alteration, leading to the initiation of cancer cells. This situation can also accelerate the development of cancer cells and metastasis. During cancer cell development, inflammatory products, such as cytokines and chemokines, facilitate the survival and proliferation of cancer cells and promote angiogenic changes that can promote cancer cell growth.<sup>16</sup>

The immune system is the body's primary defense mechanism. The immune system must recognize danger signals and respond to them. Impairment of the immune system against cancer is a classic example of the consequences of immunosenescence. Elderly individuals experience a decrease in lymphocyte production, impaired activation, signaling and proliferation of T cells, and accumulation of non-functional T cells, which make the anti-cancer response of T-cells suboptimal.<sup>16</sup>

### **Prediction of Toxicity Due to Cancer Therapy in the Elderly**

Cancer care for older adults is complex. Frequently older adults have coexisting medical and social issues that complicate cancer treatment and require additional attention. Oncologists are often faced with difficulties in planning and establishing a treatment plan in this population.<sup>19</sup> Although older and younger individuals benefit equally from the treatment, the former are at greater risk of toxicity, including serious side effects and death.<sup>20</sup> As the result, QoL rather than overall survival, is more preferred treatment goal in the older individual.<sup>21</sup> In addition, a comprehensive and multidisciplinary evaluation is needed in elderly individuals with cancer to identify the benefits and risks of toxicity due to treatment plans, including morbidity and mortality.<sup>22</sup> This multidisciplinary evaluation, known as a comprehensive geriatric assessment (CGA), provides doctors with a detailed assessment of the functional status, nutritional status, comorbidities, physical condition, psychological state, cognitive status, and social support.<sup>20</sup>

Currently, most oncologists describe the functional

status of patients regardless of age. Generally, the widely used instrument to access functional status were ECOG or KPS. However, these instruments have no description of the depth or complexity of the health problems, also the description of the treatment-related risk of toxicity.<sup>20</sup> In contrast to ECOG and KPS, comprehensive geriatric assessment (CGA) can identify the vulnerability in elderly individuals, and the results can predict morbidity and/or mortality from treatment plans in the elderly population with cancer.<sup>20</sup> Thus, the International Society of Geriatric Oncology (SIOG) recommends the G-8 instrument as an initial screening for the elderly with cancer. If needed, this initial screening will be followed by a CGA by a Geriatrician. The G-8 screening results will provide early predictions on the overall treatment plan's outcome and complications.

### Geriatric 8 Instruments (G-8)

Most elderly patients with cancer have at least one problem (which often increases) on CGA assessment, which often goes undetected by standard oncological evaluation (KPS or ECOG). These post-CGA evaluation problems are associated with an increased risk of treatment-related complications, decreased function or quality of life, and poorer survival.<sup>22</sup> However, not all older patients with cancer require complete CGA. In addition, a complete CGA also takes time and resources. Therefore, SIOG recommends the use of screening instruments to identify elderly patients with cancer who would benefit from a CGA examination.<sup>23,24</sup>

G-8 is the first screening instrument specifically designed for elderly patients with cancer. This instrument consists of eight questions covering several GA domains (**Table 1**). Overall, the G8 score ranges from 0 (very severe) to 17 (no problem at all), with a threshold value for potential frailty of  $\leq 14$ .<sup>24</sup> G-8 can help oncologists make treatment planning decisions by identifying patients who need CGA (score  $\leq 14$ ) and can predict survival and treatment-related complications through a low G-8 score.<sup>19</sup>

### Radiotherapy in the Elderly

It is widely recognized that surgery is the most effective treatment in a multimodality approach to cancer treatment for solid tumors. However, surgery on cancer is generally a surgery with serious difficulty and risk. Oncology surgeons often encounter various chronic disease conditions (comorbid), especially in elderly individuals. This condition causes an increased risk of postoperative complications (pneumonia,

delirium, urinary tract infections, and death).<sup>25,26</sup> Therefore, radiotherapy is often the first choice in elderly individuals with cancer, especially in patients at high risk for surgery.<sup>7</sup>

Radiotherapy is one of the essential modalities in cancer management, where more than 50% of cancer patients will require radiotherapy as part of cancer management.<sup>27</sup> Radiotherapy can serve as the main, adjuvant therapy along with other therapeutic modalities, such as surgery and systemic therapy. Radiotherapy can be given with a curative intent or reduce symptoms caused by cancer (palliative intent).<sup>7</sup>

In the elderly with cancer, there is a possibility that their organs and physiological reserves are not functioning optimally, so they have the potential to show more toxicity or have a higher risk of complications from RT and the combination of multimodality therapy with chemotherapy (fatigue, mucositis, xerostomia, dehydration, infection, cognitive decline and increased risk of falls). On the other hand, at the same time, elderly individuals have a less functional capacity to cope with these side effects, thereby increasing the risk of interruption/increasing duration of therapy, repopulation of cancer cells, or even therapeutic failure.<sup>28-30</sup> Examining the potential risks posed by giving RT to elderly individuals requires a complete, comprehensive understanding of the treatment goals, each patient's characteristics, and the tolerance to RT in each individual. The following are some strategies for giving RT that can be done for elderly individuals.

### Perform comprehensive screening and evaluation of elderly individuals.

Comprehensive geriatric assessment (CGA) may be a resourceful and time-consuming assessment. Hence, screening instruments are recommended in daily clinical practice to select patients who require a more thorough evaluation by a geriatrician. G-8 instrument (**Table 1**) can detect patients who may benefit from CGA. G-8 assessment is easy and fast (less than 5 minutes), can be carried out by all medical personnel, and diagnostic and predictive accuracy has been validated in large-scale studies.<sup>19</sup>

G-8 has been shown to have prognostic value for survival and patient tolerance to treatment, adding information relevant to performance status and detecting barriers that could reduce or prevent treatment benefits. After the G-8 assessment, patients should be grouped based on their physiological status into categories of fit and potentially vulnerable patients. This patient category has a different prognosis and physiological reserve to tolerate high doses of

**Table 1.** G-8 instrument for screening of elderly patients with cancer.

No	Question	Score
1	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0 severe decrease in food intake
		1 moderate decrease in food intake
		2 no decrease in food intake
2	Weight loss during the last 3 months	0 weight loss > 3 kg
		1 does not know
		2 weight loss 1-3 kg
		3 no weight loss
3	Mobility	0 bed or chair bound
		1 able to get out of bed/chair but does not go out
		2 No mobility problems
4	Neuropsychological problems	0 severe dementia or depression
		1 mild dementia or depression
		2 no psychological problems
5	Body Mass Index	0 BMI < 19
		1 BMI 19 < 21
		2 BMI 21- 23
		3 BMI ≥ 23
6	Takes more than 3 medications per day	0 yes
		1 no
7	In comparison with other people of the same age, how does the patient consider his/her health status?	0 not as good
		0.5 does not know
		1 as good
		2 better
8	Chronological age	0 ≥ 85
		1 80 – 85
		2 ≤ 80
TOTAL		
<b>Score ≤ 14: Potentially frail</b>		

Source: Reference no. 24

radiation or in combination with chemotherapy. Patients in the potential frail category have a poor prognosis, have high toxicity with standard care, and are candidates for palliative care. These patients may be candidates for interventions and treatment modifications, such as shorter hypofractionated RT treatments or the selection of low-risk chemotherapy accompanied by adjustment of a therapeutic dose.<sup>29</sup> Physiologically fit patients can tolerate more radical treatments and be treated with the same procedure as the younger patients.

### The use of RT with high imaging modalities and techniques

Radiotherapy has developed very rapidly in the last two decades, both scientifically and in the use of technology. Image-Guided Radiotherapy (IGRT), which uses Computed tomography (CT)-based 3-dimensional (3D) RT, incorporating other imaging modalities such as Magnetic Resonance Imaging (MRI) and biological imaging such as Positron

Emission Tomography (PET) in the radiation planning process, allows for improved visualization, and accuracy in targeting and dose therapy. This technique has widely replaced the 2-Dimensional RT technique.<sup>31</sup> Currently, the most widely used RT technique is Intensity-Modulated Radiation Therapy (IMRT). IMRT utilizes the movement of each MLC to deliver different radiation doses to other areas within the target volume (**Figure 2**). This technique can optimize the dose distribution the target volume and minimize the radiation dose to healthy organs. Apart from the IMRT technique, volumetric arc therapy (VMAT), where the LINAC gantry will rotate around the patient, provides a different shape and intensity of light at each angle, enabling the delivery of the dose at the desired confirmation within minutes. Stereotactic body radiation therapy (SBRT) and Stereotactic radiation therapy (SRT)/stereotactic radiosurgery (SRS) are able to allow the delivery of ablative doses with very high accuracy to tumor volumes.<sup>31</sup> These techniques have been associated with lower toxicity and are widely used

in various cancers, including head, neck, breast, and prostate cancers.<sup>28</sup>

Considering the elderly functional status and potential risk of post-therapy morbidity and mortality, the emergence of more accurate modern radiation technology has presented a safer and more efficient radiation option. In addition, the study of Pfeffer et al. also showed that elderly patients could tolerate RT better, especially with modern conformal RT techniques.<sup>31</sup> Guineau et al. also showed that modern RT can maintain or even improved overall QoL in localized prostate cancer.<sup>32</sup> Thus, the consensus from The International Geriatric Radiotherapy Group (IGRG), recommends that conformal RT techniques can be used in potentially curative and early stages elderly cancer patients.<sup>33</sup>

### Fractionation Scheme Reduction

Generally, RT dose is given in fractionation regiment, with 1.8 Gray (Gy) to 2 Gy per fraction per day. The total dose and the number of fractions planned vary based on the type and location of the tumor.<sup>34</sup> RT for curative purposes generally takes 6 – 8 weeks and is mainly administered on an outpatient scheme.<sup>31,33</sup> Hypofractionation is an RT scheme by giving higher than 2 Gy fraction doses.<sup>7</sup> Thus, administering a higher therapeutic dose per fraction will ultimately shorten the overall RT administration time.

Bearing in mind that elderly individuals are at increased risk of toxicity, this population is also at risk of not completing a lengthy radiation treatment scheme. Fatigue, decreased clinical status, increased risk of falls, and the burden of care during patient transfer can occur due to daily radiotherapy

sessions.<sup>7,28</sup> Thus, these patients would benefit from the hypofractionated scheme, which delivers the same total dose as the conventional schedule, but in a smaller number of treatment sessions (fewer visits to hospital care facilities).<sup>28</sup>

Studies on the effectiveness of the hypofractionated scheme have been carried out and resulted in comparable results to conventional fractions especially in breast cancer. Bentzen et al. and Whelan et al., in their studies, START A, START B, and Canadian trial, reported that whole breast hypofractionated compared with conventional scheme in breast cancer provided equivalent local control and survival in elderly patients.<sup>35-37</sup> In a palliative scheme, the administration of hypofractionated dose in bone metastases (1x8 Gy) had a lower incidence of acute toxicity (nausea and vomiting, diarrhea, and fatigue) than 30 Gy in 10 fractions.<sup>38</sup>

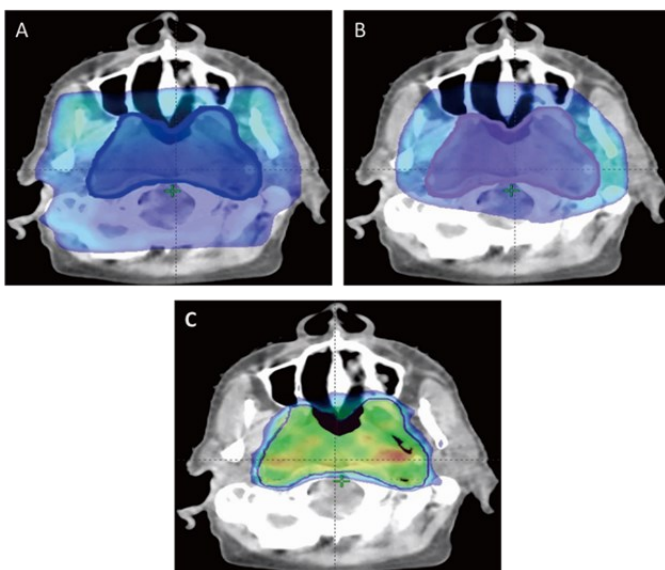
Looking at the tolerability of towards hypofractionated scheme, IGRG recommends their usage in elderly individuals with cancer. Moreover, the hypofractionation scheme is well tolerated and able to reduce the impact of fatigue as well as overcome social barriers, such as costs and distance traveled from home to radiotherapy facilities.<sup>33</sup>

### Conclusion

Caring for the elderly with cancer requires knowledge and expertise in oncological and geriatric issues. Comprehensive assessment of functional status, comorbidities, and other complicating factors is essential to be carried out in a multidisciplinary manner to minimize risks during therapy. Multidisciplinary integration between oncology and geriatrics in one individualized treatment plan can optimize therapeutic outcomes for elderly patients with cancer.

The use of assessment instruments for elderly patients in daily practice can provide a different perspective on the overall treatment plan in which survival is less important than QoL. This instrument can also predict the risks that will arise in the future and maintain or improve patients' QoL. Evaluation of this overall functional status will provide direction and aims to treat elderly individuals and families.

Radiotherapy can be a good solution in the elderly with cancer, especially in patients at high risk for systemic therapy or surgery. Radiotherapy can be given with a curative purpose or reduce symptoms caused by cancer (palliative). Radiotherapy with modern techniques and adjustment of fractionation (hypofractionation) can minimize the toxicity due to therapy and is well tolerated by the elderly.



**Figure 2.** Image-guided radiotherapy planning and dose distribution on target volume and healthy tissue. A) 2-Dimensional Planning; B) 3-Dimensional Planning; and C) IMRT planning.

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