Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 2
BBBS 2023

Prognostic analysis of 23 cases of undifferentiated thyroid carcinoma

Xin Yang

Chongqing University Cancer Hospital, Head and Neck cancer Center, Chongqing 400030, China

117289462@qq.com

Abstract. Objective: To investigate the relationship between clinical features, treatment and prognosis of undifferentiated thyroid carcinoma. Methods: The clinical and follow-up data of 23 patients with undifferentiated thyroid carcinoma admitted to Chongqing University Cancer Hospital from March 2012 to September 2019 were retrospectively analyzed. Results: The median survival time of 23 patients with undifferentiated thyroid carcinoma was 15 weeks, 3-month survival time was 56.5%, 6-month survival rate was 39.1%, and 1-year survival rate was 30.4%. Univariate analysis showed that the size of primary tumor lesion, normal albumin, normal platelets, activated partial thrombin time, fibrinogen, thyroglobulin antibody and radiotherapy were the factors influencing the prognosis of undifferentiated thyroid cancer. The analysis of the effect of treatment on the prognosis showed that surgery, radiotherapy and combined treatment can obviously improve the prognosis. Multivariate analysis showed that the independent factors affecting prognosis were the diameter of the primary lesion, whether radiotherapy was given or not, the dose of radiotherapy, and whether radiotherapy was combined with surgery. Conclusion: The malignant degree of undifferentiated thyroid cancer is very high, so R0 or R1 resection of neck lesions plus radiotherapy should be taken as far as possible for patients with surgical opportunity, and the same effect may be achieved for patients who have lost the surgical opportunity. Anticoagulant and antiplatelet therapy may benefit patients.

Key words: anaplastic thyroid carcinoma; treat; prognosis.

1. Introduction

Thyroid anaplastic carcinoma incidence is low, develops in older patients, high malignant degree and poor prognosis, the median surial only about 3 months, no clinically effective treatment methods, this study selected tumor hospital affiliated to chongqing university seven years of undifferentiated thyroid carcinoma were analyzed retrospectively, look for ways to affect the prognosis of clinical characteristics and treatment.

2. Materials and Methods

2.1. Clinical data

A total of 23 inpatients with undifferentiated thyroid cancer admitted from March 2012 to September 2019 died during hospitalization or after discharge, which was confirmed by telephone follow-up.There were 8 males and 15 females, aged 20-87 years, with a median age of 67 years.

2.2. Clinical manifestations

39.1% (9/23) had rapid onset and onset time less than 1 month; 39.1% (9/23) had airway symptoms such as hoarseness, cough, neck compression, pain and choking at admission; 52.2% (12/23) had primary lesion length greater than 4cm; 21.7% (5/23) had IVc stage with distant metastasis.43.5% (10/23) were complicated with basic cardiovascular diseases, 21.7% (5/23) were complicated with diabetes, 4.3% (1/23) were underweight index, 8.6% (2/23) were obese, 26.1% (6/23) were leukocyte count increased, and 56.5% (13/23) were complicated with anemia.13% (3/23) had increased platelet,

43.5% (10/23) had increased fibrinogen, 43.5% (10/23) had postoperative pathology Ki67≥60%, and 13% (3/23) had combined papillary carcinoma components.

2.3. Treatment and grouping

52.2% of patients (12/23) received resection of neck lesions R0 or R1 (no visible residual lesions), including thyroidectomy and tumor resection plus regional lymph node dissection. Some patients underwent more extensive surgery to remove the affected airway wall and larynx.47.8% (11/23) of the patients did not receive lesion resection, including those who had lost the opportunity of surgery or gave up treatment for other reasons upon admission, including 1 patient who only received tracheotomy.30.4% (7/23) of patients who received radiotherapy ≥50Gy, 69.6% (16/23) of patients who did not receive radiotherapy (including 3 patients whose radiotherapy was ineffective and whose disease progressed rapidly during radiotherapy and terminated radiotherapy).4.3% (1/23) received paclitaxel + platinum chemotherapy.

Considering that the actual treatment methods adopted by patients are complex and there are different single plan or comprehensive plan, the two effective treatment methods may be divided into different groups of comparison at the same time, resulting in no statistically significant difference.Therefore, in addition to single factor analysis, survival analysis of treatment factors was divided into separate groups and controlled groups: 1) simply receiving resection of neck lesions R0 or R1 and not receiving any treatment were divided into two groups;2) Radiotherapy alone (≥50Gy) and no treatment were divided into one group;3) Rapid progression and termination of the disease in radiotherapy alone were divided into two groups;4) R0 or R1 resection of cervical lesions + radiotherapy ≥50Gy were divided into the same group as R0 or R1 resection of cervical lesions alone;5) R0 or R1 resection of cervical lesions + radiotherapy ≥50Gy and radiotherapy ≥50Gy were divided into the same group.

2.4. Statistical methods

SPSS 17.0 software was used for analysis.Kaplan. Meier method was used to test log-rank survival distribution.Cox regression model was introduced for the significant variables in univariate analysis to eliminate the interfering factors between variables and establish the independent factors affecting prognosis.$P<0.05$ was considered as statistically significant difference.

3. Results and Discussion

3.1. Univariate survival analysis

All 23 patients were confirmed to have died of this disease during follow-up, with a median survival of 15 weeks, 3-month survival of 56.5%, 6-month survival of 39.1%, and 12-month survival of 30.4%.The classification is shown in Table 1.

Table 1. Univariate analysis of clinical data of 23 patients with undifferentiated thyroid carcinoma

clinical data	case number	Median survival time (weeks)	3-month survival rate (%)	6-month survival rate (%)	12-month survival rate (%)	x^2	P value
gender							
male	8	19	62.5	37.5	37.5	0.125	0.724
female	15	61.5	71.4	46.2	30.8		
age							
≥60	19	14	52.7	31.6	26.3	1.534	0.215
<60	4	51	75	75	50		
disease time							
≥1month	14	17	57.1	42.9	28.6	0.015	0.904
<1month	9	14	55.6	33.3	33.3		

Accompanying symptoms (hoarseness, cough)							
exist	9	12	44.4	22.2	22.2	0.008	0.927
without	14	22	64.3	50	35.7		
Maximum diameter of primary lesion							
≥4cm	12	10	25	25	25	5.234	0.022
<4cm	11	26	90.9	54.5	36.4		
clinical stages							
IVA	4	51	100	75	50	1.736	0.420
IVB	14	14	57.1	35.7	28.6		
IVC	5	10	20	20	20		
body mass index							
fat	2	22	50	50	0	0.115	0.990
overweight	4	11	25	25	25		
standard	16	17	62.5	43.8	37.5		
underweight	1	19	100	0	0		
Admission hemoglobin							
normal	10	13	50	30	30	0.045	0.833
lower	13	19	61.5	46.2	30.8		
Total leukocyte count on admissio							
rise	6	10	33.3	16.7	16.7	0.994	0.319
normal	17	19	64.7	47.1	35.3		
Platelet on admission							
rise	3	10	0	0	0	6.735	0.034
normal	19	19	68.4	47.3	36.8		
lower	1	10	0	0	0		
Hospital Fbg							
rise	10	11	30	0	0	10238	0.006
normal	11	32	72.3	63.6	45.5		
lower	2	99	100	100	100		
operative treatment							
Cervical lesions R0 or R1 were resected	12	29	66.7	58.3	41.7	0.564	0.453
No resection of the lesion was performed	11	11	45.5	18.2	18.2		
radiotherapy							
≥50Gy	7	156	85.7	85.7	85.7	11.775	0.001
No radiation	16	11	43.6	18.8	6.3		
chemotherapy							
Yes	1	70	100	100	100	0.132	0.716
No	22	14	54.5	36.4	27.3		
Comprehensive treatment model							
R0 or R1 resection of cervical lesions plus radiotherapy ≥50Gy	5	128	80	80	80	1.812	0.178
Other patterns	18	13	50	27.8	16.7		
Whether there is thyroid papillary carcinoma							
Yes	3	32	66.6	66.6	33.3	0.002	0.962
No	20	14	55	35	30		
Ki67							
≥60%	10	15	50	40	20	2.002	0.157
<60%	13	15	61.5	38.5	38.5		

3.2. Univariate analysis of treatment

Patients with primary tumor diameter ≤4cm, platelets in normal range and radiotherapy ≥50Gy had better prognosis.Patients with increased fibrinogen have a poor prognosis.

And sex, age, period, whether with respiratory symptoms, whether to have basic metabolism of cardiovascular diseases, body mass index, whether anemia, total number of white blood cells, clinical stage, whether surgery, surgery plus radiotherapy comprehensive treatment pattern, the chemotherapy, postoperative pathology showed whether merged thyroid papillary carcinoma, such as Ki67 is greater than 60% has nothing to do with the prognosis.See table 1.

Survival analysis of treatment factors was performed separately in groups and controls.According to the analysis results, 1) survival time of patients who only received resection of neck lesions R0 or R1 was significantly better than that of patients who did not receive any treatment; 2) survival time of patients who only received radiotherapy ≥50Gy was significantly better than that of patients who did not receive any treatment.3) Patients who received neck lesions R0 or R1 resection + radiotherapy ≥50Gy were significantly better than those who only received neck lesions R0 or R1 resection + radiotherapy ≥50Gy. 4) There was no significant difference between patients who only received neck lesions R0 or R1 resection + radiotherapy ≥50Gy and patients who received neck lesions R0 or R1 resection + radiotherapy ≥50Gy. 5) Only received radiotherapy but radiotherapy was ineffective.There was no significant difference between those who stopped treatment because of rapid disease progression and those who did not receive any treatment.See Table 2, Figure 1-7.

Table 2. Effect of different treatment options on prognosis of undifferentiated thyroid carcinoma

Treatment of classification	case number	Median survival time (weeks)	3-month survival rate (%)	6-month survival rate (%)	12-month survival rate (%)	x^2	P value
R0 or R1 were resected							
R0 or R1 resection of cervical lesions was performed alone	7	19	57.1	42.9	14.3	4.804	0.028
No treatment was given	9	6	33.3	0	0		
radiotherapy							
Radiotherapy alone ≥50Gy	2	201	100	100	100	5.039	0.025
No treatment was given	9	6	33.3	0	0		
Invalid radiotherapy							
Rapid progression of the disease terminated with radiotherapy alone	2	6	0	0	0	0.328	0.567
No treatment was given	7	11	42.9	0	0		
Comprehensive treatment 1							
R0 or R1 resection of cervical lesions plus radiotherapy ≥50Gy	5	128	80	80	80	4.628	0.031
R0 or R1 resection of cervical lesions alone	7	19	57.1	42.9	14.3		
Comprehensive treatment 2							
R0 or R1 resection of cervical lesions plus radiotherapy ≥50Gy	5	128	80	80	80	2.047	0.153
Radiotherapy alone ≥50Gy	2	201	100	100	100		

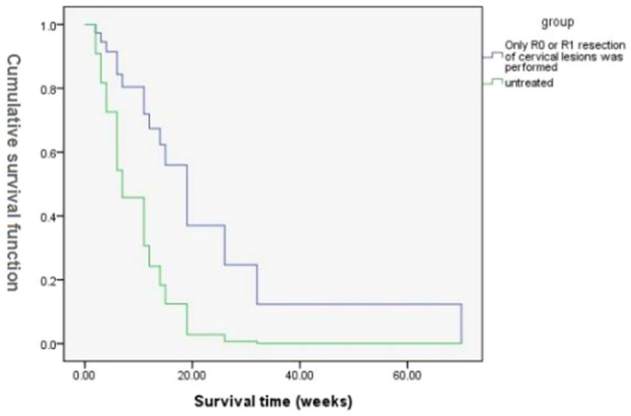

Figure 1. Effect of different treatment options on prognosis of undifferentiated thyroid carcinoma (1)

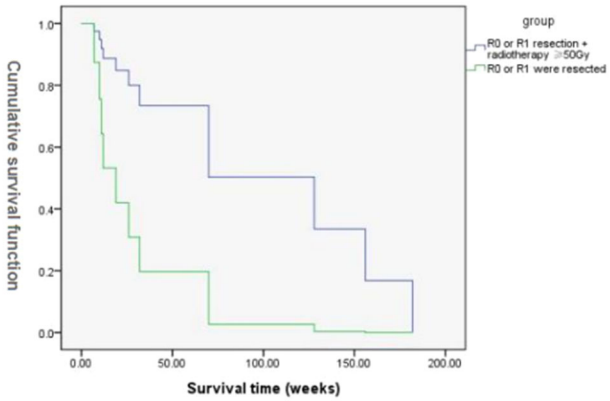

Figure 2. Effect of different treatment options on prognosis of undifferentiated thyroid carcinoma (2)

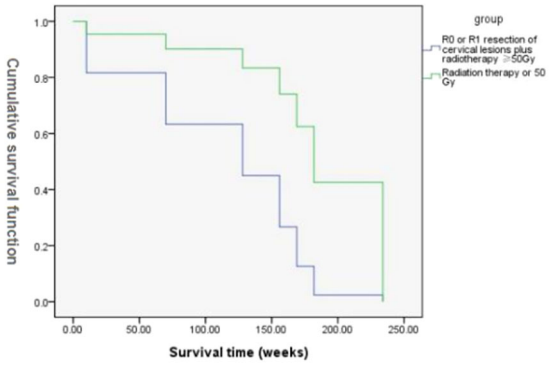

Figure 3. Effect of different treatment options on prognosis of undifferentiated thyroid carcinoma (3)

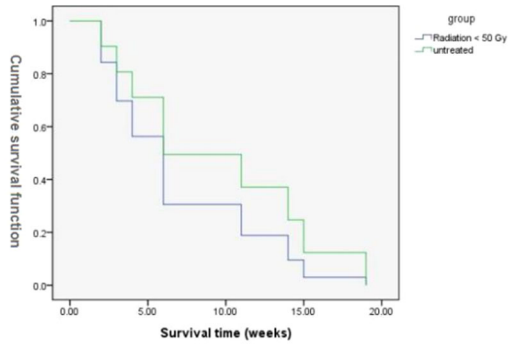

Figure 4. Effect of different treatment options on prognosis of undifferentiated thyroid carcinoma (4)

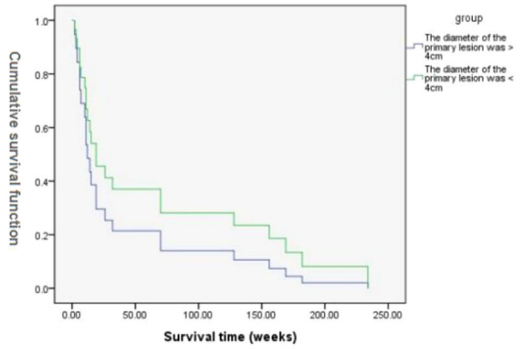

Figure 5. Effect of different treatment options on prognosis of undifferentiated thyroid carcinoma (5)

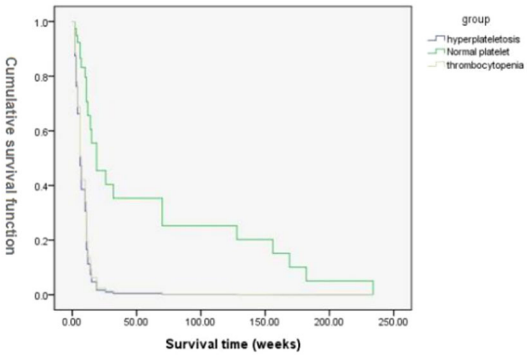

Figure 6. Effect of different treatment options on prognosis of undifferentiated thyroid carcinoma (6)

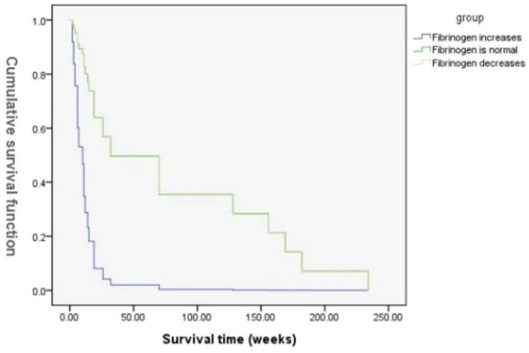

Figure 7. Effect of different treatment options on prognosis of undifferentiated thyroid carcinoma (7)

3.3. Multi-factor analysis

whether the primary lesion diameter, radiation therapy, radiation dose, whether surgery combined radiotherapy Cox regression model, introduced the four factors, found the primary lesion diameter greater than 4 cm, accepted radiotherapy, radiotherapy dose than 50 gy, surgery combined radiotherapy ($P < 0.05$) is to determine the thyroid anaplastic carcinoma prognosis is good independent factors, as shown in table 3.

Table 3. Multifactorial analysis of prognosis of ATC

variate	regression coefficient	standard error	Wald value	P value	relative risk	OR value 95% confidence limit	
						lower limit	upper limit
Diameter of primary lesion	1.000	.453	4.881	.027	2.719	1.119	6.606
radiotherapydose	-2.350	.791	8.819	.003	.095	.020	.450
Whether the radiation	-1.278	.617	4.283	.038	.279	.083	.935
Whether surgery combined with radiotherapy	-1.662	.838	3.928	.047	.190	.037	.982

4. Conclusions

This study found that the incidence of undifferentiated thyroid cancer in this group accounted for 3% of thyroid cancer in the same period, and the prognosis was poor. The median survival time was only 15 weeks, and the 1-year survival rate was only about 30%.The majority of patients are aged, with a median age of 67 years old. Most patients are complicated with cardiovascular and cerebrovascular diseases and metabolic diseases such as hypertension and diabetes at the time of onset, with many complications. In addition, the disease progresses rapidly.Among the subjects in this study, age advantage less than 60 years old did not translate into survival advantage, and there were no significant differences in the combination of underlying diseases and cardiovascular metabolic diseases, nutritional status, anemia, white blood cell count, etc.This suggests that for undifferentiated thyroid cancer, earlier tumor detection and effective treatment strategies are the key factors to improve the prognosis of patients compared with other factors related to systemic conditions.

Undifferentiated thyroid cancer has a high degree of malignancy, rapid tumor growth, large primary lesion on admission, and often accompanied by invasion of adjacent tissues and organs. Clinically, it is difficult to distinguish it from other types of locally advanced thyroid cancer, and puncture cytology often fails to make a clear diagnosis, which causes difficulties in the selection of treatment.Literature has suggested that surgery, radiation and chemotherapy of consolidation comprehensive treatment to prolong surial for patients with thyroid anaplastic carcinoma [1] [2] [3], in addition, relevant guidelines also suggested that for locally advanced thyroid cancer, lesions relatively have higher chance to important structures around may adhesion, invasion, such as the larynx, trachea, esophagus, carotid blood vessels and laryngeal recurrent nerve.The scope of surgical resection for such lesions has always been controversial, but the removal of visible tumors is very important for controlling local recurrence of tumors and prolonging the survival of patients.Studies have shown that 5-year disease-specific survival rates of patients with locally advanced DTC undergoing R0 (complete resection with negative margin) and R1 (positive margin) resection were 94.4% and 87.6%, respectively, while R2 (visible residual lesion) resection significantly decreased, and 5-year disease-specific survival rate was only 67.9%[4].Therefore, no matter what type, surgery is preferred whenever there is an opportunity.As undifferentiated thyroid tumor malignant degree is high, often had invasion with the surrounding tissue from the primary lesion and metastasis lymph node merge into pieces, no boundaries, so for the operation, the choice of either do not visible to the naked eye remains complete removal of lesion, or not to remove, it's hard to do only palliative excision part, and another part of kuang.We doubt for thyroid anaplastic carcinoma patients with imaging and surgery tolerance ability assessment, in patients with cervical lesions complete resection can be removed, all

did R0 or R1 resection, scope of operation in addition to the thyroid and tumor, adjacent muscles, regional lymph nodes, and part of the wider surgery patients,Part of the trachea wall and throat were excised.Of course, the patients who did not receive surgery were not only unable to undergo surgery, but also concerned about risk or gave up treatment due to other factors.

In this retrospective study, R0 or R1 resection improved the survival of patients compared with those who did not receive any treatment (including those who could be operated but gave up treatment for other reasons) (Figure 1), and the difference in survival was statistically significant.Furthermore, the survival time of patients who had received resection of neck lesions R0 or R1 and received further radiotherapy with a dose greater than or equal to 50Gy was further improved compared with surgery alone (Figure 2), and the difference between the two was statistically significant.These results suggest that, first of all, R0 or R1 resection is effective in improving the prognosis of undifferentiated thyroid carcinoma, and the combined treatment mode of surgery and radiotherapy is significantly better than surgery alone in improving the prognosis.In addition we found the lost the operation chance and choose pure radiation therapy in some patients, they accepted the greater than or equal to 50 gy of radiation therapy, the prognosis analysis and surgery plus radiation therapy did not differ between the integrated model (figure 3), this may indicate if radiation effectively, surgery is not necessary, even the close to report related conclusion [2].But this is based on the premise of effective radiation, because once the radiotherapy is invalid, and did not receive any treatment outcomes did not differ between the patients (according to our research and analysis, only accept radiation therapy, but radiotherapy is invalid, the treatment is terminated due to the rapid progression, and did not receive any treatment there was no statistically significant difference between the survival patients) (figure 4).However, whether a tumor is sensitive to radiotherapy cannot be predicted before treatment, but only based on the response after treatment.Therefore, it is suggested that patients who have the opportunity of surgery should first choose surgical resection of the lesion to ensure at least the basic curative effect. If conditions permit, postoperative radiotherapy should be performed as far as possible to achieve a better prognosis.For patients who have lost the opportunity of surgery on admission, it is recommended to choose radiotherapy alone, and whether to perform tracheotomy before or during treatment according to the situation to avoid airway compression caused by edema. If radiotherapy is effective, these patients may obtain the same or similar prognosis as the combined treatment.There was only 1 patient with postoperative combined chemotherapy. Although the individual with paclitaxel + platinum had a good prognosis, there was no statistical significance.

This retrospective study showed that in the thyroid anaplastic carcinoma, different points during tumor prognosis, there was no significant difference, and the median survival time is the shorter of the relevant literature reports, this may be due to more, because of all sorts of reasons to give up treatment combined with effective treatments for patients with stage another part of the higher don't intervene the result together.In this group of samples, there were few IVc stage samples, and some of them received complete comprehensive treatment, which improved the prognosis.

In this study, there was a significant difference in prognosis between the group with primary lesion larger than 4cm and the group with primary lesion smaller than 4cm at the time of diagnosis (Figure 5).Due to the high degree of malignancy and strong invasions of undifferentiated thyroid cancer, the vast majority of tumors larger than 4cm are prone to invade the surrounding muscles (T3b) or adjacent organs and large blood vessels (T4) except for a very small number of T3a tumors. As a result, patients with excessively large primary lesions have no chance of surgery or surgical difficulties resulting in incomplete resection.There is a rapid recurrence and progression of the tumor in a short period of time and ultimately death of the patient.In follow-up cases, this data immediately after the primary lesions in the treatment of recurrent or progress, festering infection, airway pressure or neck tumor is most of the major causes of death in the short term after onset, contrary to the primary lesion progress after treatment to effectively control regardless of whether there is a distant metastasis, and the survival time is relatively long.Therefore, for patients with undifferentiated thyroid cancer, it is very important to control the local progression of the primary tumor, which can achieve a better prognosis, which is the same as the treatment strategy for patients with locally advanced DTC [4].

As a systemic disease, the prognosis of malignant tumor may be related to the systemic condition.This review found that patients with elevated platelets had a worse prognosis than those with normal platelets (Figure 6).Platelets also play an important role in the occurrence and development of tumor cells. Platelets can promote tumor cell growth, metastasis, escape immune surveillance and improve invasion ability and angiogenesis in a variety of ways [5]. For example, by secreting transforming growth factor -β, tumor cell metastasis ability is enhanced [6].By secreting adenosine diphosphate, cancer cells can easily penetrate blood vessels and metastasize [7].Platelets can also release granuloprotein and interact with activated platelets and prostaglandins on blood vessels to increase vascular permeability and promote the degradation of surrounding tumor tissues and metastasis [8].And malignant tumor cells increase in the number of cytokine that promotes cancer growth such as IL - 1, IL - 3, tumor necrosis factor alpha and so on, the possibility to stimulate thrombocytosis [9-10], at the same time, the body in order to repair the damage, compensatory hyperplasia, bone marrow will lead to new platelet number increase, and increase of platelet in turn promote tumor growth,This is a vicious cycle [11-13]. It has been reported that inflammation and thrombocytopenia can be used as one of the indicators to evaluate the disease progression and prognosis of patients with colorectal cancer [14].One patient with thrombocytopenia also showed a very poor prognosis, but the patient's survival was only 10 weeks. Systemic failure at the end stage of the tumor may lead to thrombocytopenia, at which time thrombocytopenia may be a result of tumor development rather than a cause.

This review found that some of the measures related to coagulation function also caused significant differences in outcomes, with patients with increased Fbg showing worse outcomes (Figure 7).Fibrinogen is a glycoprotein with a molecular weight of 340 kD. It is synthesized and secreted by hepatocytes and consists of two pairs of α, β and γ chains.There are small peptides called fibrin A and fibrin B at the n-terminus of α and β peptide chains respectively, and fibrin A and B are specifically excised by thrombin to form polymeric reticulated fibrin monomers [15].Fibrinogen is mainly involved in the coagulation process of the body. Meanwhile, under the action of thrombin, its degradation products can provide stable adhesion and metastasis scaffold for tumor cells, so that tumor cells are easy to grow, metastasize and invade blood vessels to form tumor thrombi or tumor nuclear matrix [16-17]. Meanwhile, it not only promotes the formation of secondary tumors,Moreover, it also helps tumor cells escape the killing of therapeutic drugs [18-19], which are associated with poor prognosis of various malignant tumors.Relevant studies have found that plasma fibrinogen level in cancer patients is significantly higher than that in benign disease patients, and the level of fibrinogen is significantly increased during tumor recurrence or metastasis [20].The plasma fibrinogen of hepatocellular carcinoma patients is higher than that of hepatitis B cirrhosis patients, and the original fibrinogen value also increases with the increase of TNM stage [21].Other literatures have reported that high fibrinogen level often predicts shorter survival and poorer prognosis in cancer patients [22-23].

Cancer patients often combined high coagulation state, and the conventional anti-tumor treatment including surgery, radiotherapy and chemotherapy are to varying degrees of increase high coagulation state, resulting in the risk of blood clots in malignant tumor is a tumor of about 7 times [24], studies have shown that not only indicates poor prognosis of patients with malignant tumor thrombosis, high mortality,And can increase the risk of cancer in patients with non-malignant tumors.This indicates that epidemiology has a bidirectional relationship between malignant tumor and coagulation, and that coagulation function system plays an important role and significance in the development of malignant tumor [25].

In summary, for the treatment of patients with undifferentiated thyroid cancer, we can draw the following conclusions: 1) Early diagnosis and treatment are recommended. The smaller the primary lesion, the better the prognosis.2) For patients with surgical opportunity, first try for surgery, R0 or R1 resection of neck lesions has a better prognosis.3) Patients who have received surgery should try their best to receive postoperative radiotherapy, and the dose should be greater than or equal to 50Gy.4) For patients who have lost the opportunity of surgery or are contraindicated with surgery upon

admission, radiotherapy may obtain the same or similar prognosis as comprehensive treatment after the pathological diagnosis is confirmed.5) Radiotherapy is an independent factor affecting prognosis, and should not be abandoned unless patients are too poor to tolerate radiotherapy.Anticoagulant and antiplatelet therapy may benefit patients, but its guiding significance for clinical management remains to be studied.

Conflicts Of Interest

The author declare that they have no conflicts of interest.

Acknowledgments

Xin YANG conceived the study, collected and analyzed the data, and is critically revised the article for important intellectual content. The author read and approved the final copy of the manuscript for publication.

References

[1] Iwao Sugitani, Akira Miyauchi, Kiminori Sugino, et a1. Prognostic factors and treatment outcomes for anaplastic thyroid carcinoma: ATC Research Consortium of Japan cohort study of 677 patients. [J]. World J Surg.2012 Jun;36(6):1247-54.

[2] Swaak-Krarglen AT, de Wilt JH, Sehmitz PI, et a1. Muhimadallty treatment for anaplastic thyroid carcinoma-Treatment outcome in 75 patients. Radiother Oncol, 2009, 92: 100-104.

[3] Chandrakanth Are, Ashok R Shaha. Anaplastic thyroid carcinoma: biology, pathogenesis, prognostic factors, and treatment approaches [J]. Ann Surg Onco.2006 Apr; 13(4):453-64.

[4] Wang LY, Nixon IJ, Patel SG, et al. Operative management of locally advanced, differentiated thyroid cancer. Surgery, 2016, 160(3): 738-46.

[5] Sebastian Szubert, Rafal Moszynski, Dariusz Szpurek, et al.The expression of Platelet-derived Growth factor receptors (PDGFRs) and their correlation with overall survival of patients with ovarian cancer[J]. Ginekol Pol.2019; 90(5): 242-249.

[6] Labelle M, Begum S, Hynes RO. Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis[J]. Cancer cell, 2011, 20(5): 576-590.

[7] Schumacher D, Strilic B, Sivaraj KK, et al. Platelet-derived nucleotides promote tumor-cell transendothelial migration and metastasis via P2Y2 receptor[J]. Cancer cell, 2013, 24(1): 130-137.

[8] Hammad Bhatti, Avinash Ramdass, James D Cury, et al. Operator dependent factors implicated in failure of non-invasive positive pressure ventilation (NIPPV) for respiratory failure[J]. Clin Respir J. 2017 Nov; 11(6): 901-905.

[9] Zhongxing Liang, Joann Brooks, Margaret Willard, et al. CXCR4/CXCL12 axis promotes VEGF-mediated tumor angiogenesis through Akt signaling pathway [J]. Biochem Biophys Res Commun. 2007 Aug 3; 359(3): 716-22.

[10] Xiaofei Li, Jun Qiu, Min Pan, et al. Small peptide inhibitors of the CXCR4 chemokine receptor (CD184) antagonize the activation, migration, and antiapoptotic responses of CXCL12 in chronic lymphocytic leukemia B cells [J]. Blood.2005 Sep 1; 106(5): 1824-30.

[11] Meike Burger, Tanja Hartmann, Myriam Krome, et al. Correlation between congenital heart disease complicated with pulmonary artery hypertension and circulating endothelial cells as well as endothelin-1[J]. Int J Clin Exp Pathol. 2015 Sep 1; 8(9): 10743-51.

[12] Jing-Xia Zhang, Hong-Zhi Dong, Bing-Wei Chen, et al. Characteristics of coronary arterial lesions in patients with coronary heart disease and hypertension[J]. Springerplus.2016 Jul 29; 5(1): 1208.

[13] Shashank Jain, John Harris, Jerry Ware Platelets: linking hemostasis and cancer[J]. Arterioscler Thromb Vasc Biol.2010 Dec; 30(12): 2362-7..

[14] Karen V Winther, Tine Jess, Ebbe Langholz, et al. Long-term risk of cancer in ulcerative colitis: a population-based cohort study from Copenhagen County[J]. Clin Gastroenterol Hepatol. 2004 Dec; 2(12): 1088-95.

[15] Tuba İnal, Ceyda Anar, Gülru Polat, et al. The prognostic value of D-dimer in lung cancer [J]. Clin Respir J.2015 Jul; 9(3): 305-13.

[16] Gloria de la Red, Dolores Tàssies, Gerard Espinosa, et al. Factor XIII-A subunit Val34Leu polymorphism is associated with the risk of thrombosis in patients with antiphospholipid antibodies and high fibrinogen levels [J]. Thromb Haemost. 2009 Feb; 101(2): 312-6.

[17] Adams GN, Rosenfeldt L, Frederick M, et al. Colon cancer growth and dissemination relies upon thrombin,stromal PAR-1, and fibrinogen[J]. Cancer Research, 2015, 75(19): 4235–4243.

[18] Grigoris T Gerotziafas, Chryssoula Papageorgiou, Mohamed Hatmi. et al. Clinical studies with anticoagulants to improve survival in cancer patients [J]. Pathophysiol Haemost Thromb. 2008; 36(3-4): 204-11.

[19] Grigoris T Gerotziafas, Chryssoula Papageorgiou, Mohamed Hatmi. et al. Clinical studies with anticoagulants to improve survival in cancer patients[J]. Pathophysiol Haemost Thromb2008; 36(3-4): 204-11.

[20] Xuefeng Yu, Fulan Hu, Qiang Yao, et al Serum fibrinogen levels are positively correlated with advanced tumor stage and poor survival in patients with gastric cancer undergoing gastrectomy: a large cohort retrospective study [J]. BMC Cancer, 2016 Jul 14; 16:480.

[21] Guo-Ying Wang, Nan Jiang, Hui-Min Yi, et al Pretransplant Elevated Plasma Fibrinogen Level is a Novel Prognostic Predictor for Hepatocellular Carcinoma Recurrence and Patient Survival Following Liver Transplantation[J]. Ann Transplant. 2016 Feb 23; 21: 125-30.

[22] Sabine Krenn-Pilko, Uwe Langsenlehner, Tatjana Stojakovic, et al An elevated preoperative plasma fibrinogen level is associated with poor disease-specific and overall survival in breast cancer patients[J]. Breast, 2015 Oct; 24(5): 667-72.

[23] Wei-Yu Xu, Hao-Hai Zhang, Xiao-Bo Yang, et alPrognostic significance of combined preoperative fibrinogen and CA199 in gallbladder cancer patients [J]. World J Gastroentero, 2018 Apr 7; 24(13): 1451-1463.

[24] Agnes Y Y Lee. Management of thrombosis in cancer: primary prevention and secondary prophylaxis[J]. Br J Haematol, 2005, 128(3): 291–302.

[25] Antonis Vylliotis, Christos Yapijakis, Emeka Nkenke, et al Effect of thrombosis-related gene polymorphisms upon oral cancer: a regression analysis [J]. Anticancer Res, 2013 Sep; 33(9): 4033-9.