Università degli studi di Napoli "Federico II"

Scuola di Medicina e Chirurgia

Dipartimento di Scienze Biomediche Avanzate

Direttore: Prof. Alberto Cuocolo

Dottorato in Scienze biomorfologiche e chirurgiche
(XVVV ciclo)

Coordinatore: Prof. Alberto Cuocolo

Long-term prognostic value of response to therapy assessed 12 months after radioiodine treatment in pediatric patients with Differentiated Thyroid Cancer.

Relatore
Ch.mo Prof. Michele Klain

Candidato
Dott.ssa Mariarosaria Manganelli

Index

Abstract

Purpose. Differentiated thyroid tumors (DTC) account for 21% of all head and neck cancer in pediatric patients with an increasing incidence rate of approximately 1% annually. Unlike adults, children typically present with advanced disease at diagnosis. In particular, extensive regional nodal involvement and distant metastases are more frequent in children as compared to adult patients. Moreover, disease recurrence after initial treatment occurs more frequently in young patients, leading to a high rate of reoperation. Despite this, prognosis in pediatric patients with DTC is excellent, with an overall survival of 90% at 30 years. Although death from DTC is low, the best treatment strategy in pediatric patients is still debating. According to ATA guidelines, 131-Iodine (131-I) therapy is routinely performed in patients with DTC. In pediatric patients, DTC are usually highly iodine avid, and show an excellent response to radioiodine therapy. Several authors have reported improved survival, decreased disease progression, and lower recurrence rates in those with advanced DTC who received postoperative radio- active iodine (RAI). Aim of this study is to evaluated the prognostic value of the 12-month response to therapy after initial treatment with surgery and radioactive iodine (RAI) in pediatric patients with differentiated thyroid cancer (DTC).

Methods. We retrospectively evaluated 94 pediatric patients with DTC, treated with surgery and RAI who were initially classified as low, intermediate or high risk of recurrence according to the American Thyroid Association (ATA) guidelines. Twelve months after RAI administration the response to therapy was assessed by serum thyroglobulin (Tg) measurement and neck ultrasound and patients were classified as having excellent response (ER) or no-ER.

Results At the 12 months evaluation, 62 (66%) patients had ER and 32 (34%) no-ER. During a mean follow-up time of 86 months (range 9-517), 19 events occurred (20% cumulative event rate). Events occurred more frequently in younger patients ($p < 0.05$), in those at ATA

intermediate/high risk ($p < 0.01$) and with a pre-RAI therapy Tg level >10 ng/mL ($p < 0.001$), and in those with no-ER ($p < 0.001$). At multivariate analysis, the evidence of no-ER was the only independent predictor of events.

Conclusion. In pediatric patients with DTC, the response to therapy evaluated 12 months after initial treatment has an independent prognostic impact and is able to predict mid-term outcome which very often coincides with the long-term one. Patients with no-ER at 12 months after RAI therapy should be closely followed-up.

Introduction

Differentiated thyroid cancer (DTC) is quite rare in children [1, 2] accounting for 21% of all head and neck cancer in pediatric patients with an increasing incidence rate of approximately 1% annually. Unlike adults, children typically present with advanced disease at diagnosis. The initial treatment consists in surgery followed by radioactive iodine (RAI) therapy in selected patients [3]. DTC usually presents as a more extended disease in children and adolescents than in adult patients, with extensive regional nodal involvement and more frequent lung metastases, but the survival rate at 30 years is close to 90% [4-6]. The rate of recurrence is high in pediatric patients, in particular in those with high post-operative serum thyroglobulin (Tg) values [7, 8]. The American Thyroid Association (ATA) risk stratification classification may help to recognize at the time of initial treatment patients with a high risk of persistent/recurrent disease [9]. On the other hand, the extent of nodal disease is defined according to central or lateral location of lymph node involvement [9]. To refine this classification some authors considered the criteria used in the adult ATA guidelines, such as the number and size of the metastatic lymph nodes [7, 10, 11]. This modified ATA risk stratification was able to predict the outcome in pediatric DTC patients [10, 11]. In addition, a dynamic risk stratification system based on biochemical and imaging data that evaluates the response to initial therapy at 12 months predicted the outcome in adult patients [12, 13]. However, this prognostic approach has not been fully addressed in children.

The aim of this study was to evaluate the prognostic role of the response to therapy assessed at 12 months after initial treatment in pediatric patients with DTC.

Materials and methods

Study population

We retrospectively evaluated 122 pediatric DTC patients (age <18 years) referred to our Department between 1992 and 2010. All patients underwent a total thyroidectomy, with or without central and/or lateral neck dissection, followed by RAI therapy. Before RAI administration, L-thyroxine was discontinued until the serum thyroid stimulating hormone (TSH) level has increased above 30 mIU/l. At the time of RAI, serum thyroglobulin (Tg) was determined and a ^{131}I activity according to the body weight and the amount of disease (37 to 111 MBq/Kg) was administered. From 1992 to 1996, serum Tg levels were determined by an immunoradiometric assay (Dynotest Tg, Henning, Berlin, Germany) with a sensitivity of 1 ng/mL. From 1997, Tg was determined by a chemiluminescence system (Immulite, Diagnostic Products Corp, Los Angeles, CA, USA) with a detection limit of 0.2 ng/mL. According to post-operative Tg values obtained at the time of RAI therapy, patients were categorized into two groups: >10 ng/ml and ≤10 ng/ml [7, 14]. Five to seven days after ^{131}I administration, a post-therapy whole body scan (WBS) was performed as previously described using a dual-head gamma camera (E.CAM, Siemens Medical Systems, Hoffman Estates, IL, USA) equipped with thick crystals and high energy collimators [15].

ATA initial risk stratification

The risk of recurrence was initially estimated according to histopathological findings and the results of ^{131}I post-therapeutic WBS, based on ATA pediatric guidelines [9]. Patients were classified as low risk (disease grossly confined to the thyroid, with N0 or Nx disease or with incidental N1a metastasis), intermediate risk (extensive N1a or minimal N1b disease) or high risk (extensive N1b disease or T4 tumor with gross tumor extension beyond the thyroid capsule,

with or without distant metastasis). To consider nodal involvement as extensive, we used the number and size of lymph nodes, for N1b >5 or any lymph node metastases ≥3 cm or the presence of any clinically detected lymph node metastases, according to the ATA adult guidelines [10, 11].

Therapy response evaluation

The response to therapy at 12 months after RAI administration was assessed with serum Tg measurement obtained on LT4 treatment or following thyroid hormone withdrawal, neck ultrasound and imaging findings which can result from a CT, a PET-CT, a MRI or from a WBS performed at 2 days after intake of 5 mCi of 131-I with suspension of L-thyroxine 21 days before or administration of rh-TSH without suspending hormone replacement therapy. Patients without neck ultrasound at the 12-month evaluation were excluded from the study. According to the 2015 ATA guidelines for adults [10], definitions of response to therapy were: (1) excellent response (ER), negative imaging and either Tg <0.2 ng/mL on LT4 treatment or TSH-stimulated Tg <1 ng/mL; (2) indeterminate response, non-specific findings on imaging studies and Tg levels on LT4 treatment that are detectable but <1 ng/mL or stimulated Tg levels between 1 and 10 ng/mL or stable or declining titer of anti-Tg antibodies over time; (3) biochemical incomplete response, negative imaging and Tg ≥1 ng/mL on LT4 treatment or stimulated Tg ≥10 ng/mL or rising titer of anti-Tg antibody over time (4) structural incomplete response, structural evidence of disease with any level of serum Tg or of anti-Tg antibodies.

Follow-up

After the evaluation at 12-months, patients were followed every 6-12 months with serum Tg determinations (on L-thyroxine and in some patients off L-thyroxine therapy) and with imaging procedures. Disease status was recorded at each evaluation. Recurrence of disease was defined

by histology or imaging procedures; suspicious nodal abnormalities at neck ultrasonography were confirmed by fine needle aspiration cytology and Tg determination in the aspirate fluid, histology or presence of RAI uptake; uptake in the thyroid bed at post-therapy WBS was considered structural disease only when it corresponded to abnormal findings at neck ultrasonography [10]. Patients last known to be alive and without structural disease were censored at the date of last contact.

Statistical analysis

Continuous data are expressed as mean ± standard deviation and categorical data as percentage. Student's two-sample *t* test and χ^2 test were used to compare the differences in continuous and categorical variables, respectively. Univariate and multivariate logistic regression analyses were performed to identify the variables associated with 12 months response to initial treatment. Hazard ratios with 95% confidence intervals (CI) were also calculated by univariate and multivariate Cox regression analyses. Variables showing a *p* value <0.05 at univariate analysis were considered for multivariate analysis. Disease free survival analysis was performed using the Kaplan-Meier method and log-rank test. Statistical analysis was performed with Stata 12 software (StataCorp, College Station, Texas USA).

Results

Among 122 pediatric patients with DTC, 28 without serum Tg determinations and/or neck ultrasound at the 12-months evaluation were excluded, leaving 94 subjects for the analysis. At initial evaluation, 62 (66%) patients were classified as ATA low risk, 17 (18%) as ATA intermediate risk and 15 (16) as ATA high risk. Of these latter patients at high risk, 3 had lung metastases at post-therapy WBS.

At the 12 months evaluation, 62 (66%) patients had ER to initial therapy and 32 (34%) no-ER (Table 1). Among the no-ER patients, 11 were classified as indeterminate response, 17 as biochemical incomplete response and 4 as structural incomplete response for lung metastases (n = 3) or for lymph node metastases (N1b) confirmed by fine needle aspiration biopsy (n = 1). The 3 patients with lung metastases underwent a second RAI treatment and the patient with lymph node metastases was treated with surgery. Among the 32 no-ER patients, 15 (47%) were initially classified as ATA low risk and 17 (53%) as ATA intermediate/high risk. Serum Tg at the time of RAI treatment was >10 ng/mL in 25 (78%) no ER patients. Twelve (37%) patients were younger than 14 years at the time of initial treatment (Table 1). At multivariate logistic regression analysis, a pre-therapy Tg >10 ng/mL was the only independent predictor of no-ER ($p < 0.001$) (Table 2).

Predictors of outcome

During a median follow-up of 86 months (range 9-517 months), 19 events occurred (20% cumulative event rate): 12 patients required additional RAI therapy, 6 for recurrence in the thyroid bed, 4 for recurrence in both thyroid bed and lymph nodes and 2 for lung metastases. The other 7 patients underwent both additional surgery and RAI therapy for nodal disease.

Patients with events were younger at initial treatment ($p < 0.05$), had a higher prevalence of ATA intermediate/high risk ($p<0.01$) and pre-therapy Tg >10 ng/mL ($p < 0.001$) (Table 3). The

rate of events was significantly higher in the 32 patients with no-ER (n = 16, 50%) at 12 months as compared to the 62 patients with ER (n = 3; 5%) ($p < 0.001$). At multivariate Cox analysis (Table 4), no-ER remained the only independent predictor of events ($p < 0.001$).

At Kaplan Meier analysis, the disease free survival was lower in patients with no-ER as compared to those with ER (177 ± 32 vs. 477 ± 23 months, $p < 0.001$). The worst prognosis was observed in patients with no-ER and intermediate/high ATA risk (Fig. 1) and in patients with no-ER and pre-therapy Tg >10 ng/mL (Fig. 2) (both $p < 0.001$).

Discussion

In this retrospective analysis, we found that the response to initial treatment evaluated at 12 months with serum Tg determination and neck ultrasound, is able to predict the mid-term and generally long-term outcome of pediatric DTC patients treated with surgery and RAI.

At initial diagnosis, pediatric patients with DTC present with more extensive disease as compared to adults, but the survival rate at 30 years close to 90% [1-4, 16], and most patients with lung metastases will experience an excellent response to RAI therapy [6]. However, the rate of recurrence is higher in pediatric than in adult patients, especially in those with multifocal papillary thyroid cancer, with gross tumor extension beyond the thyroid capsule and in those with extensive lymph node involvement [18]. Pediatric patients with pre-RAI therapy Tg levels >10 ng/ml have a higher risk of structural recurrence, in particular those classified as ATA intermediate risk [8, 9, 19]. The initial risk stratification in pediatric patients with DTC is performed according to pediatric ATA guidelines, where the extent of nodal disease is defined according to central or lateral location of lymph node involvement [9]. We used a refined classification considering the criteria used in the adult ATA guidelines, such as the number and size of the metastatic lymph nodes [7, 11], and this modified ATA risk stratification was able to predict outcome in a cohort of 260 children with DTC [11]. In adult patients the dynamic risk stratification has been proposed to evaluate the response to therapy during follow-up. The addition of laboratory and imaging findings obtained during the first 12-24 months after treatment, can improve the initial risk assessment in adult patients [13] and also in pediatric patients [8, 19].

In this retrospective analysis of 94 pediatric patients, 62 (66%) were initially classified as ATA low risk. At 12 months evaluation, most (76%) of these low risk patients, had an ER, in agreement with the series of Sapuppo et al. [11]. However, the other 15 (24%) low-risk patients

had no-ER, suggesting that a further stratification in these patients is needed. From our results it emerged that, despite no-ER was more frequent in younger patients, the presence of pre-therapy Tg values >10 ng/mL was the only independent predictor of no-ER. Predicting 12 months response to treatment is crucial, considering that the presence of no-ER is associated with unfavorable outcome. In our series, the rate of events was higher in no-ER patients, and the presence of no-ER remained the only independent predictor of outcome at multivariable analysis. Interestingly, lung metastases were observed in only 3 patients at diagnosis. Despite the evidence of structural incomplete response at 12-month evaluation and the need for a second RAI treatment, at the end of follow-up two of these patients had an excellent response to treatment. Indeed, the rate of recurrence was higher in patients with biochemical incomplete response at 12 months.

In adult patients with low-risk thyroid cancer, the probability of persistent disease is low in patients with low or undetectable post-operative TSH stimulated Tg level, and the benefits of RAI administration have been recently questioned [20, 21]. This approach should be further investigated in low risk children in order to reduce their irradiation whenever it is not beneficial. On the contrary, in patients initially at higher risk, the evaluation at 12-months might better identify patients in whom a more aggressive follow-up is needed.

Conclusions

Our data suggest that in pediatric patients with DTC the response to therapy evaluated 12 months after initial treatment has an independent prognostic impact and is able to predict mid-term and almost always the long-term one . Patients with no-ER at 12 months after RAI therapy should be closely followed-up.

References

1. Lamartina L, Leboulleux S, Schlumberger M. Thyroid cancer incidence in children and adolescents. Lancet Diabetes Endocrinol. **9**, 128-129 (2021)
2. Hogan AR, Zhuge Y, Perez EA, Koniaris LG, Lew JI, Sola JE. Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients. J Surg Res. **156**, 167-172 (2009)
3. Borson-Chazot F, Causeret S, Lifante JC, Augros M, Berger N, Peix JL. Predictive factors for recurrence from a series of 74 children and adolescents with differentiated thyroid cancer. World J Surg. **28**, 1088-1092 (2004)
4. Hay ID, Johnson TR, Kaggal S, Reinalda MS, Iniguez-Ariza NM, Grant CS et al. Papillary thyroid carcinoma (PTC) in children and adults: comparison of initial presentation and long-term postoperative outcome in 4432 patients consecutively treated at the Mayo Clinic during eight decades (1936-2015). World J Surg. **42**, 329-342 (2018)
5. Hay ID, Gonzalez-Losada T, Reinalda MS, Honetschlager JA, Richards ML, Thompson GB. Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008. World J Surg. **34**, 1192-1202 (2010)
6. Pawelczak M, David R, Franklin B, Kessler M, Lam L, Shah B. Outcomes of children and adolescents with well-differentiated thyroid carcinoma and pulmonary metastases following ^{131}I treatment: a systematic review. Thyroid. **20**, 1095-1101 (2010)
7. Klain M, Zampella E, Manganelli M, Gaudieri V, Nappi C, D'Antonio A et al. Risk of structural persistent disease in pediatric patients with low or intermediate risk differentiated thyroid cancer. Endocrine. **71**, 378-384 (2021)
8. Cistaro A, Quartuccio N, Garganese MC, Villani MF, Altini C, Pizzoferro M et al. Prognostic factors in children and adolescents with differentiated thyroid carcinoma treated with total thyroidectomy and RAI: a real-life multicentric study. Eur J Nucl Med Mol Imaging. **49**, 1374-1385 (2022)

9. Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenga S, Cerutti JM et al. American Thyroid Association Guidelines Task Force. Management Guidelines for children with thyroid nodules and differentiated thyroid cancer. Thyroid. **25**, 716-759 (2015)
10. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE et al. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. **26**, 1-133 (2016)
11. Sapuppo G, Hartl D, Fresneau B, Hadoux J, Breuskin I, Baudin E et al. Differentiated thyroid cancer in children and adolescents: long term outcome and risk factors for persistent disease. Cancers (Basel). **13**, 3732 (2021)
12. Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. Thyroid. **20**, 1341-1349 (2020)
13. Klain M, Zampella E, Piscopo L, Volpe F, Manganelli M, Masone S et al. Long-term prognostic value of the response to therapy assessed by laboratory and imaging findings in patients with differentiated thyroid cancer. Cancers (Basel). **13**, 4338 (2021)
14. Pace L, Klain M, Salvatore B, Nicolai E, Zampella E, Assante R et al. Prognostic role of 18F-FDG PET/CT in the postoperative evaluation of differentiated thyroid cancer patients. Clin Nucl Med. **40**, 111-115 (2015)
15. M. Klain, L. Pace L, E. Zampella, T. Mannarino, S. Limone, E. Mazziotti et al. Outcome of patients with differentiated thyroid cancer treated with 131-Iodine on the basis of a

detectable serum thyroglobulin level after initial treatment. Front Endocrinol (Lausanne). **10**, 146 (2019)

16. O'Gorman CS, Hamilton J, Rachmiel M, Gupta A, Ngan BY, Daneman D. Thyroid cancer in childhood: a retrospective review of childhood course. Thyroid **20**, 375-380 (2010)
17. Rivkees SA, Mazzaferri EL, Verburg FA, Reiners C, Luster M, Breuer CK et al. The treatment of differentiated thyroid cancer in children: emphasis on surgical approach and radioactive iodine therapy. Endocr Rev. **32**, 798-826 (2011)
18. Lee YA, Jung HW, Kim HY, Choi H, Kim HY, Hah JH et al. Pediatric patients with multifocal papillary thyroid cancer have higher recurrence rates than adult patients: a retrospective analysis of a large pediatric thyroid cancer cohort over 33 years. J Clin Endocrinol Metab. **100**, 1619-1629 (2015)
19. Redlich A, Luster M, Lorenz K, Lessel L, Rohrer TR, Schmid KW et al. Age, American Thyroid Association risk group, and response to therapy are prognostic factors in children with differentiated thyroid cancer. J Clin Endocrinol Metab. **107**, e165-e177 (2022)
20. Schlumberger M, Leboulleux S, Catargi B, Deandreis D, Zerdoud S, Bardet S et al. ESTIMABL1: Favorable outcome after ablation in low risk thyroid cancer patients. Lancet Diab Endocrinol. **6**, 618-626 (2018)
21. Leboulleux S, Bournaud C, Chougnet CN, Zerdoud S, Al Ghuzlan A, Catargi B et al. Thyroidectomy without radioiodine in patients with low-risk thyroid cancer. N Engl J Med. **386**: 923-932 (2022)

Tables

Table 1 Baseline characteristics according to the 12-months response to initial treatment

	All patients (*n* = 94)	No-ER (*n* = 32)	ER (*n* = 62)	*p* value
Age (years)	16 ± 2	15 ± 3	16 ± 2	0.34
Age ≤14years, *n* (%)	23 (25)	12 (37)	11 (1)	<0.05
Male gender, *n* (%)	24 (26)	12 (37)	12 (20)	0.06
ATA risk categories				
Low risk, *n* (%)	62 (66)	15 (47)	47 (76)	<0.01
Intermediate/high risk, *n* (%)	32 (34)	17 (53)	15 (24)	<0.01
Follicular type, *n* (%)	6 (6)	4 (12)	2 (3)	0.08
Tumor size >2 cm, *n* (%)	58 (62)	25 (78)	33 (53)	<0.05
Neck dissection, *n* (%)	66 (70)	25 (78)	41 (66)	0.23
Lymph node involvement, *n* (%)	57 (61)	24 (75)	33 (53)	<0.05
Time interval surgery/RAI therapy (days)	135 ± 159	142 ± 153	132 ± 162	0.77
Administered ^{131}I activity (MBq)	3182 ± 958	3182 ± 999	3182 ± 962	0.96
Pre-therapy Tg (ng/ml)	31 ± 61	63 ± 81	13 ± 29	<0.001
Pre-therapy Tg >10 ng/ml, *n* (%)	39 (41)	25 (78)	14 (23)	<0.001
Uptake at WBS, *n* (%)	92 (98)	31 (97)	61 (98)	0.63
Neck, *n*		31	61	
Extra-neck, *n*		3	0	

Data are presented as mean ± SD or number and percentage (%)

Tg thyroglobulin, *WBS* post-therapy whole body scan

Table 2 Univariate and multivariate logistic regression analyses with 12 months no-ER as dependent variable

	Univariate		Multivariate	
	Odds ratio (95% CI)	*p value*	Odds ratio (95% CI)	*p value*
Age ≤14 years	2.42 (0.91-6.45)	0.07		
Intermediate/high risk	3.55 (1.43-8.78)	<0.001	2.50 (0.87-7.15)	0.09
Tg >10 ng/mL	12.2 (4.38-34.2)	<0.001	7.04 (3.74-30.3)	<0.001

Tg thyroglobulin obtained following thyroid hormone withdrawal before the RAI administration

Table 3 Baseline characteristics according to the occurrence of events

	Event (n = 19)	No event (n = 75)	p value
Age (years)	15 ± 3	16 ± 2	0.62
Age ≤14years, *n* (%)	8 (40)	15 (20)	<0.05
Male gender, *n* (%)	6 (32)	18 (24)	0.49
ATA risk categories			
Low risk, *n* (%)	6 (32)	56 (75)	<0.01
Intermediate/high risk, *n* (%)	13 (68)	19 (25)	<0.01
Follicular type, *n* (%)	2 (11)	4 (5)	0.41
Tumor size >2 cm, *n* (%)	14 (74)	44 (59)	0.23
Neck dissection, *n* (%)	16 (84)	50 (67)	0.14
Lymph node involvement, *n* (%)	16 (84)	41 (55)	<0.05
Time interval surgery/RAI therapy (days)	125 ± 145	139 ± 162	0.74
Administered ^{131}I activity (MBq)	3367 ± 814	3136 ± 984	0.36
Pre-therapy Tg (ng/ml)	74 ± 90	19 ± 45	<0.001
Pre-therapy Tg >10 ng/ml, *n* (%)	16 (84)	23 (31)	<0.001
Uptake at WBS, *n* (%)	18 (95)	74 (99)	0.29
Neck, *n*	18	74	
Extra-neck, *n*	3	0	

Data are presented as mean ± SD or number and percentage (%)

Tg, thyroglobulin; *WBS*, post-therapy whole body scan.

Table 4 Univariate and multivariate predictors of recurrence of disease

	Univariate		Multivariate	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age ≤14 years	2.38 (0.95-5.92)	0.06		
Intermediate -High ATA risk	4.62 (1.75-12.1)	<0.01	2.22 (0.79-6.22)	0.13
Tg >10 ng/mL	9.25 (2.69-31.8)	<0.001	2.35 (0.51-30.3)	0.27
No-ER vs. ER	14.2 (4.11-48.7)	<0.001	6.99 (1.61-30.3)	<0.001

Tg thyroglobulin obtained following thyroid hormone withdrawal before the RAI administration, *ER* excellent response

Figure legends

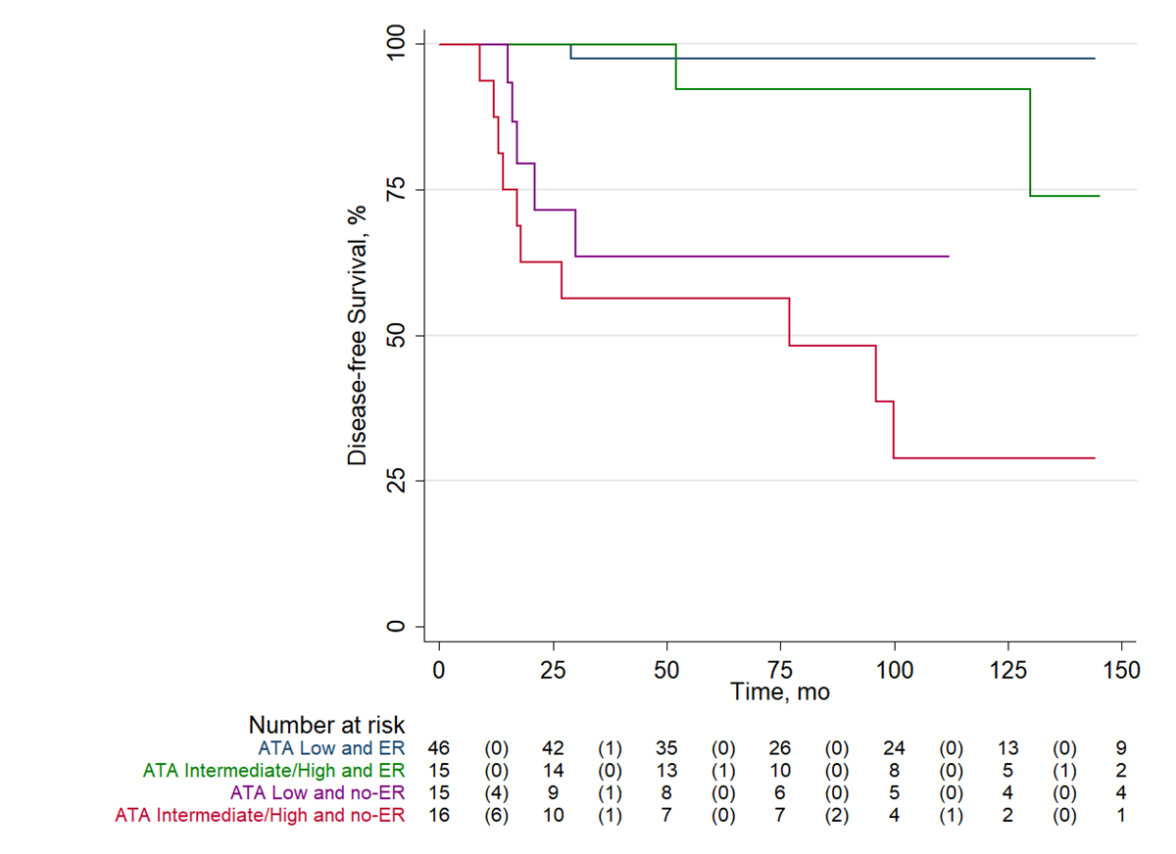

Fig. 1 Disease free survival by Kaplan-Meier according to 12-month response to therapy and ATA risk. Patients with no-ER and intermediate/high ATA risk had the worst outcome compared to the other groups ($p < 0.001$).

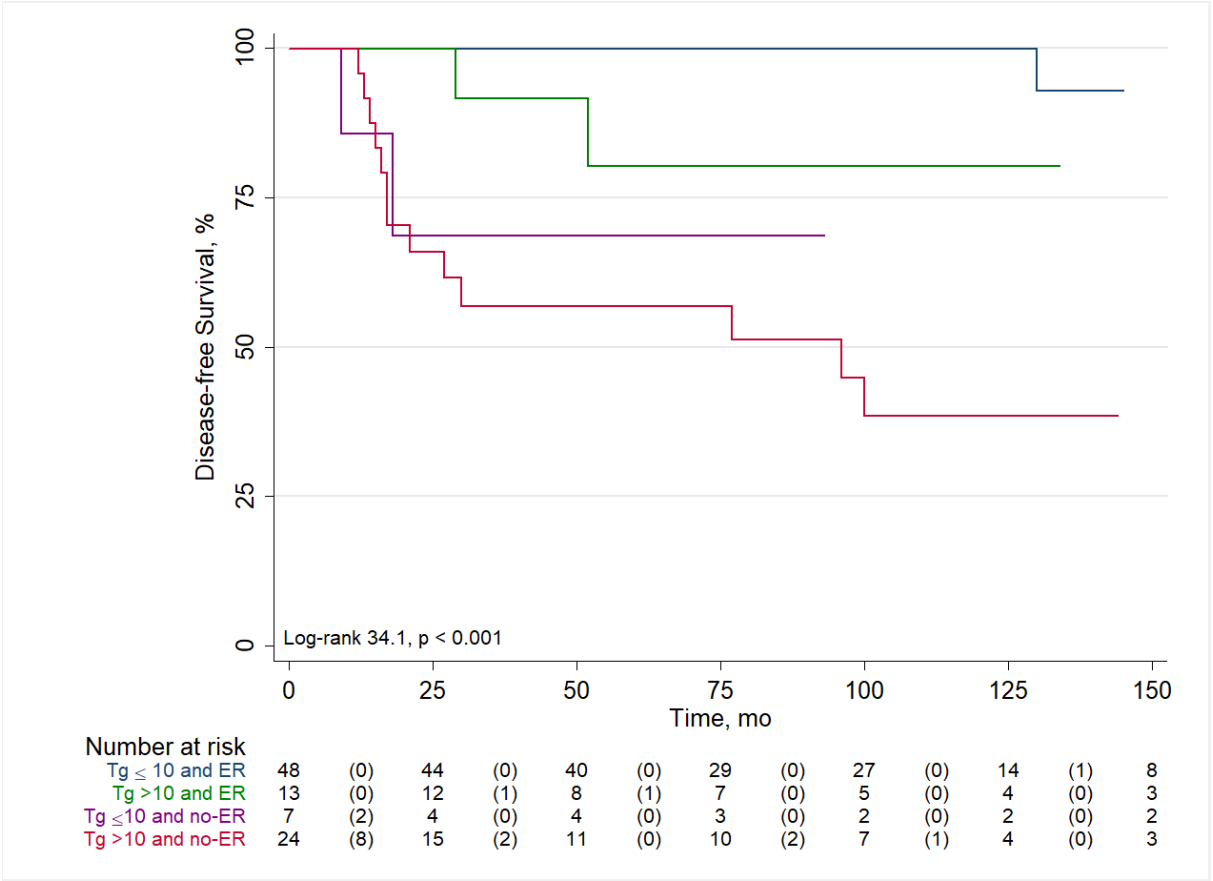

Fig. 2 Disease free survival by Kaplan-Meier according to 12-month response to therapy and post-operative serum Tg levels. Patients with no-ER and pre-therapy Tg >10 ng/mL had the worst outcome compared to the other groups ($p < 0.001$).