

# CHEMOTHERAPY EFFECTIVENESS IN THE TREATMENT OF NON-MEDULLARY WELL-DIFFERENTIATED THYROID CANCER (DTC-RAI): A SYSTEMATIC AND CASE REVIEW

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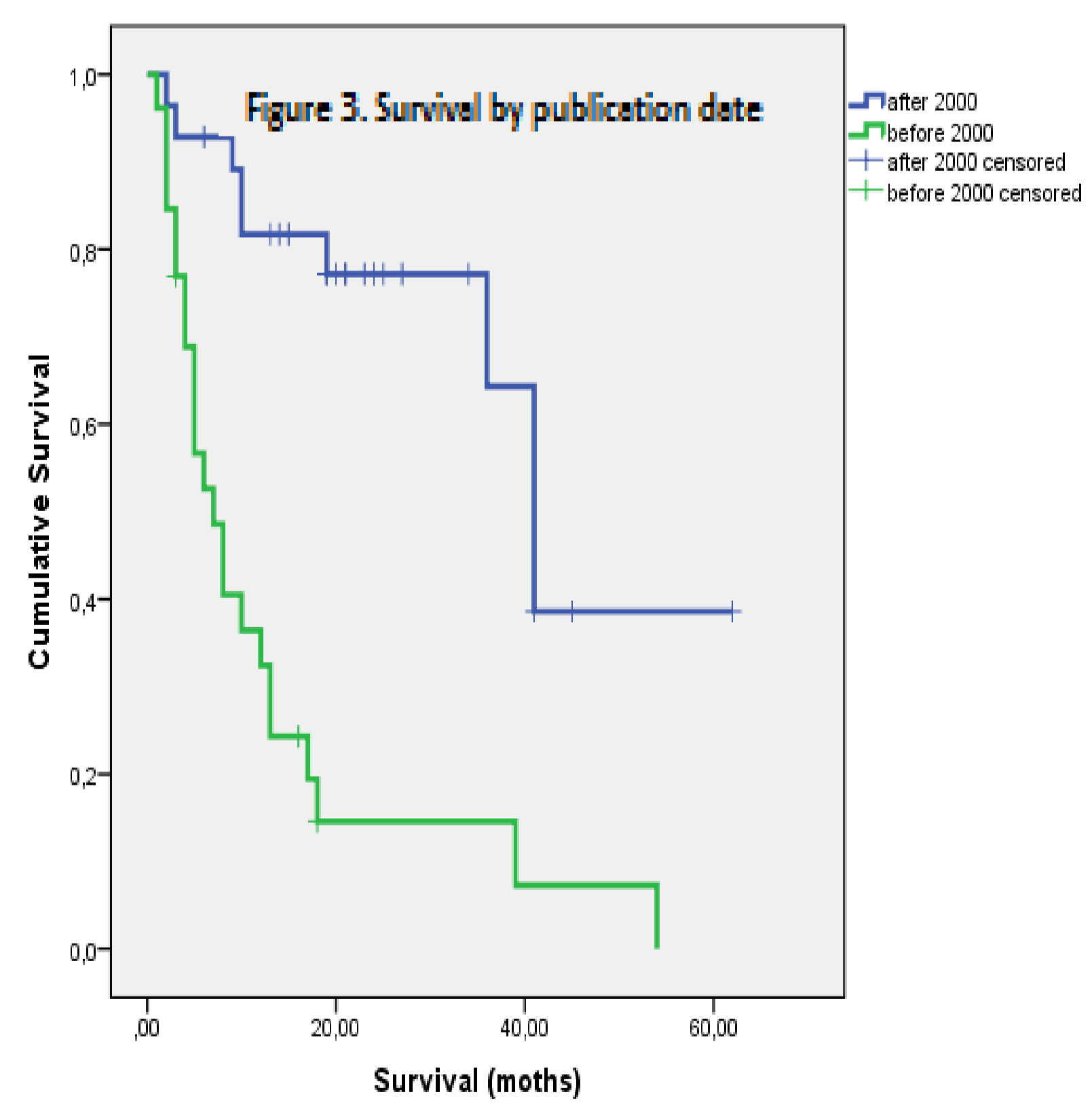
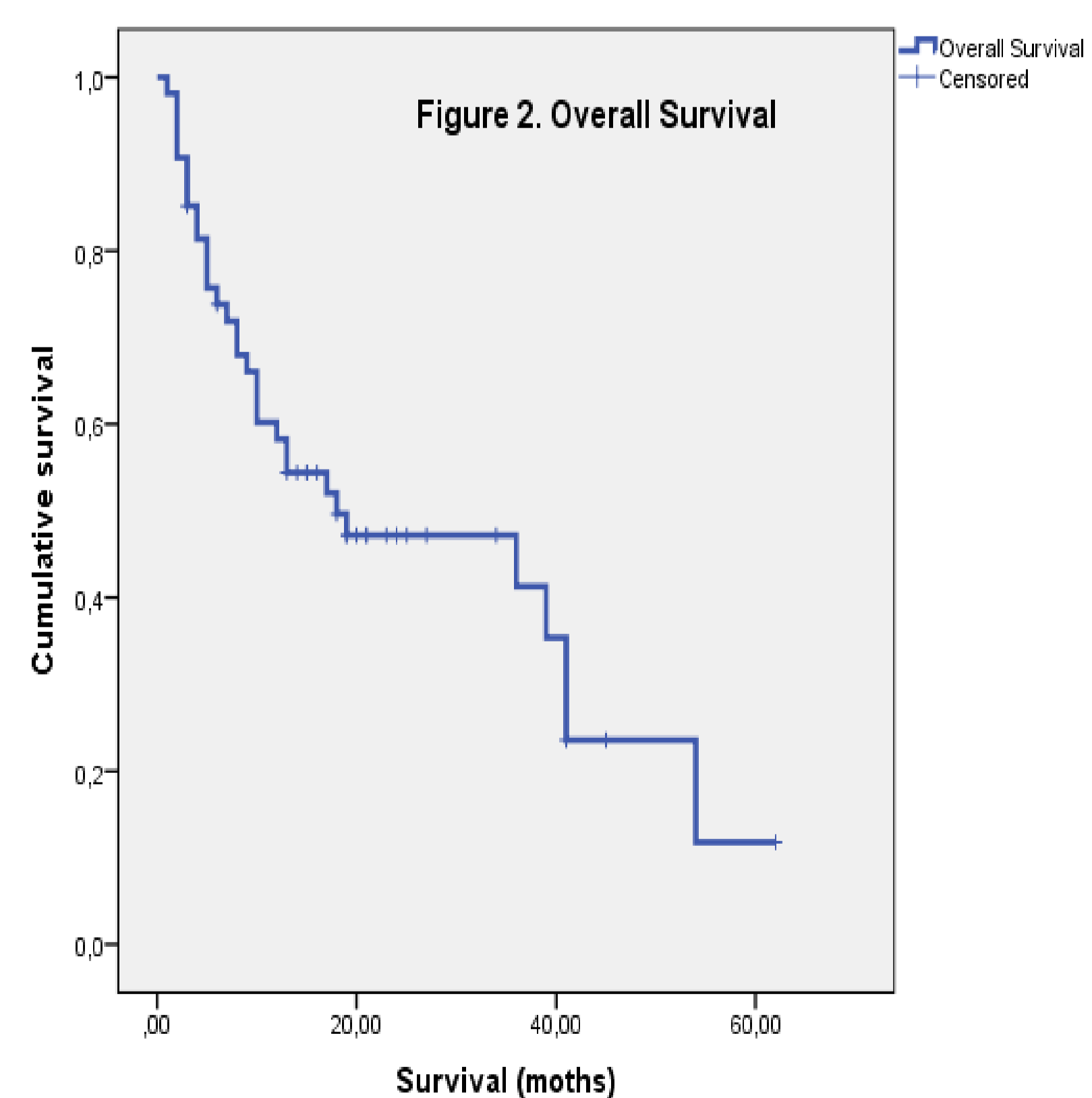
**Introduction:** Nowadays, use of chemotherapy in well-differentiated non medullary thyroid cancer, locally advanced stage and/or with radioiodine-refractory metastases is considered of scanty value. However, in the last 40 years was not published any phase III study nor a systematic review of its use in clinical setting.

**Methods:** A systematic literature search was performed in databases such as Medline and Embase, among others. Two independent reviewers analyzed the articles selected full text, made a critical reading and extracted results using forms designed specifically. A qualitative synthesis of the results was performed and the accumulated data were calculated.

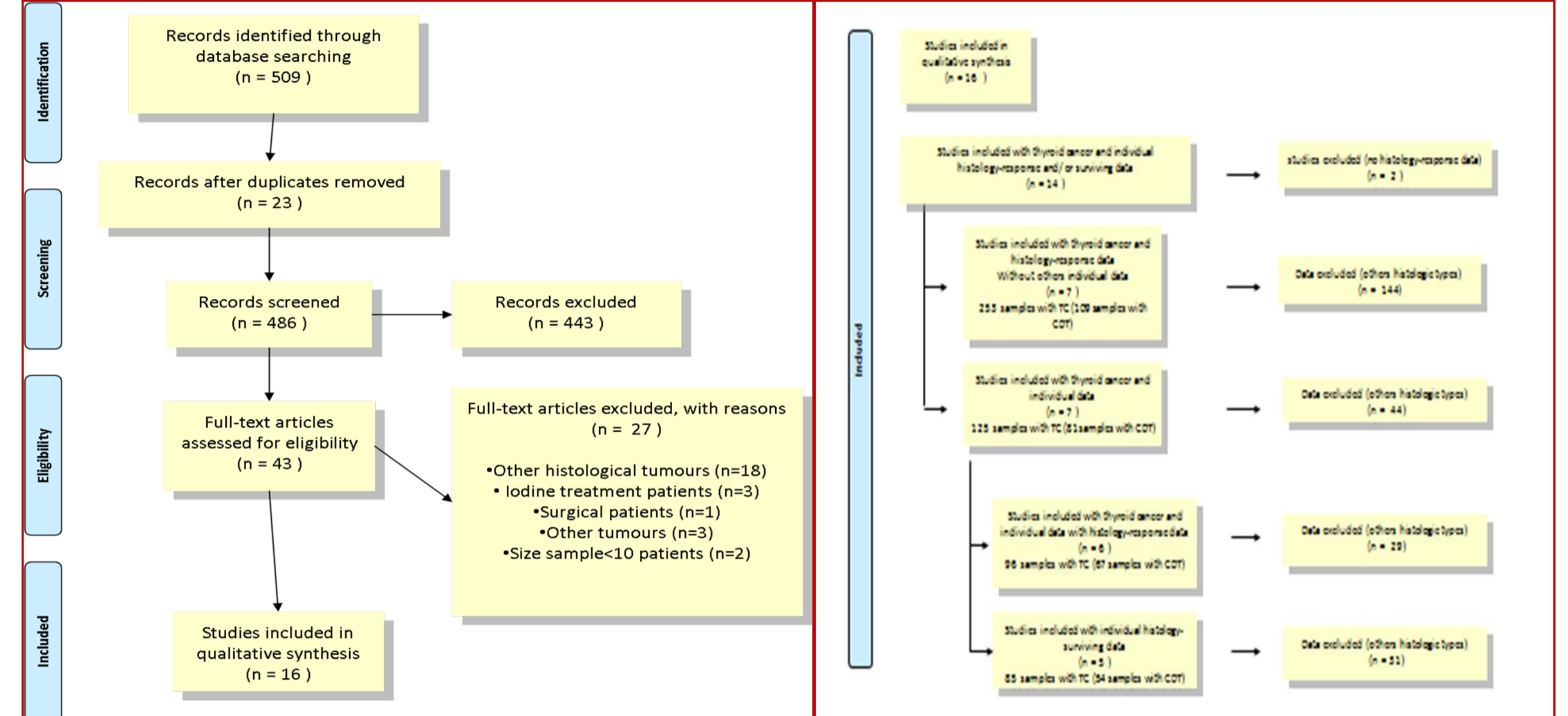
**Table 1.- Characteristics of studies included in the analysis**

Studies without other individual data, year					
	Type of study	Treatment scheme	Number of patients	Number of DTC-RAI (% de DTC-RAI)	% First-line treatment
Gottlieb, 1974 <sup>28</sup>	SD	ADM	30	15 (50%)	80
Benker, 1983 <sup>23</sup>	SD	ADM+BLM/ADM	52	21 (50%)	100
Shimaoka, 1985 <sup>20</sup>	RCT	ADM frente a ADM+CDDP	84	35 (42%)	92,9
Williams, 1986 <sup>33</sup>	SD	ADM+CDDP+VDS	28	7 (32%)	100
De Besi, 1991 <sup>25</sup>	SD	ADM+CDDP+BLM	22	8 (36%)	100
Scherubl, 1990 <sup>31</sup>	SD	ADM+CDDP+VDS	20	8 (40)	85
Argiris, 2008 <sup>21</sup>	SD	ADM+IF	17		100
Studies with individual data, year					
	Type of study	Treatment scheme	Number of patients	Number of DTC-RAI (% de DTC-RAI)	% First-line treatment
Hoskin, 1987 <sup>29</sup>	SD	Secuential monotherapy Etoposide (VP16) Carboplatino CDDP ABC Metotrexate	29	14	100 65,5 100 17,2 17,2
Schlumberger, 1989 <sup>32</sup>	SD	Mitoxantrona	17	7 (41%)	100
Matuszczyk, 2008 <sup>35</sup>	SD	ADM	19	19 (100%)	100
Benker, 1977 <sup>22</sup>	SD	ADM+BLM + Dactinomicina mantenimiento	21	8 (38%)	100
Bukowski, 1983 <sup>24</sup>	SD	ADM+VCR+BLM+MLF	11	5 (45%)	100
Santini, 2001 <sup>27</sup>	SD	Carboplatino+4epiADM	14	14 (100%)	85,7
Spano, 2012 <sup>36</sup>	SD	GEMOX	14	14 (100%)	100

RCT (randomized clinical trial), SD (descriptive series); ADM (adriamycin); CDDP (cisplatin); BLM (bleomycin); VDS (vindesine); IF (interferon alfa); VCR (vincristine); MLF (melphalan); VP (VP-16); 5FU (5-fluorouracil); CLF (cyclophosphamide); GEMOX (gemcitabine + oxaliplatin); ABC (adriamycin + vincristine + bleomycin)



**Figure 1. PRIMA flow diagram**



**Results:** A total of 509 references were found in the last 40 years. Sixteen studies involving 473 patients published were included. Thirteen studies (176 patients) showed individual response data to treatment and histology, and six of them (67 patients) showed individual data of age, sex, histology, metastatic localizations and response, among others variables (Figure 1) Characteristic of studies included showed in Table 1.

✓ In 176 patients treated with different chemotherapy alone or in combination, the **overall response rate (RR) was 25%** with a 3,4% of patients showed a complete response (CR). Eight studies reported data response relative to histologic subtype. The RR for the 39 cases with papillary cancer was 25,64% and 32,75% (5,1% CR) of 58 with follicular cancer (Table 2) Results in 67 individual patients and clinical benefit CB) shows in Tables 3. However, data must be interpreted carefully due to the risk of bias detected. Unlike modern studies, a performance status >2 was described in about 40% of patients.

✓ Five studies published individual survival data from 54 patients with advanced differentiated thyroid cancer: the **median survival was estimated at 18 months** (95% CI 0-37.5), with significant differences between patients treated before 2000 versus those treated later (7 vs 41 months, P<0.00) in multivariate analysis (Figures 2-3)

**Table 2.- Response Rate (RR). Total data**

Total data	Patients n, %	NV n, %	CR n, %	PR n, %	CR+PR n, RR	SD+PG n, %
DTC-RAI	176	5	6	38	<b>44</b>	127
Papillary DTC-RAI	100%	2,84%	3,4%	21,59%	<b>25%</b>	72,15%
Follicular DTC-RAI	39	1	1	9	<b>10</b>	28
	100%	2,56%	2,56%	23,07%	<b>25,64%</b>	71,79%
	58	2	3	16	<b>19</b>	37
	100%	3,44%	5,1%	27,58%	<b>32,75%</b>	63,79%

**Table 3.- Response Rate (RR) and Clinical Benefit (CB). Individual data**

Individual data	Patients n, %	NV n, %	CR n, %	PR n, %	CR+PR n, RR	SD n, %	RC+RP+SD n, CB	PG n, %	NR
DTC-RAI	67	1	4	15	<b>19</b>	23	<b>42</b>	21	3
	100%	1,5%	5,9%	22,38	<b>28,35%</b>	34,32%	<b>62,68%</b>	31,34%	4,47%
Papillary DTC-RAI	28	0	1	6	<b>7</b>	13	<b>20</b>	6	2
	100%	0%	3,6%	21,4%	<b>25%</b>	46,42%	<b>71,42%</b>	21,42%	7,14%
Follicular DTC-RAI	32	1	3	9	<b>12</b>	9	<b>21</b>	9	1
		3,12%	9,37%	28,1%	<b>37,5%</b>	28,12%	<b>65,62%</b>	28,12%	3,12%

DTC-RAI (differentiated non-medullary refractory radioiodine thyroid cancer); NV (Unavailable); CR (complete response); PR (partial response); RR (response rate = CR + PR/total number of patients); SD (stable disease); CB (clinical benefit = CR + PR + SD / total number of patients); PG (disease progression); NR (Not response)

In seven patients isn't reported papillary or follicular histological subtype

**Conclusion:** There are insufficient data to evaluate the effectiveness of chemotherapy in patients with advanced non medullary thyroid cancer, although it seems to have some efficacy, therefore, it could be necessary to be tested in well-designed studies versus or in combination with new therapies.

