Review

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The effects of reoperations due to inadequate treatment in differentiated thyroid cancers on morbidity, mortality and costs

Diferansiye tiroid kanserlerinde yetersiz tedavi nedeniyle yapılan reoperasyonların morbidite, mortalite ve maliyetlere etkisi

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Abstract

Although the incidence of differentiated thyroid cancer (DTC) is high, mortality is quite low. In low and intermediate risk DTCs, reoperations due to inadequate treatment can increase morbidity, mortality, and costs in patients. In our study, current articles published on this subject were reviewed and evaluated. According to our results, morbidity, mortality and costs increase due to inadequate treatment in DTCs. Therefore, even in low and intermediate risk DTC cases, adequate surgeries such as total or near total thyroidectomy should be performed by high volume endocrine surgeons and moderate TSH suppression should be applied in all cases.

Keywords: Effects, reoperations, differentiated, thyroid, cancers.

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Öz

Diferansiye tiroid kanseri (DTK) insidansı yüksek olmakla birlikte mortalitesi oldukça düşüktür. Düşük ve orta riskli DTK'lerinde yetersiz tedavi nedeniyle yeniden yapılan ameliyatlar hastalarda morbidite, mortalite ve maliyetleri artırabilir. Çalışmamızda bu konuda yayınlanmış güncel makaleler incelenip değerlendirilmiştir. Sonuçlarımıza göre, DTK'lerinde yetersiz tedavi nedeniyle morbidite, mortalite ve maliyetler artmaktadır. Bu nedenle, düşük ve orta riskli DTK vakalarında bile, yüksek hacimli endokrin cerrahlar tarafından total veya totale yakın tiroidektomi gibi yeterli ameliyatlar yapılmalı ve tüm vakalarda orta derecede TSH supresyonu uygulanmalıdır.

Anahtar kelimeler: Etkileri, reoperasyonlar, diferensiye, tiroid, kanserleri.

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Introduction

According to GLOBACAN data, the incidence of DTC is 4 and mortality is 0.5 per hundred thousand in the world [1].

The classical approach in the treatment of DTC cases is surgery, RAI and TSH suppression. Although the primary treatment is reoperation in cases of residual or recurrent DTC, some new treatment methods such as percutaneous ablation and external radiotherapy are also applied under the guidance of ultrasonography [2].

Although there is general consensus among thyroid specialists regarding the indications for RAI treatment, there are dilemmas regarding the extent of surgical treatment and the necessity of TSH suppression. In cases of DTC that are inadequately treated, reoperation is performed due to residual cancer tissue or relapses, resulting in increased cost, morbidity and mortality, and psychological problems. For this reason, studies on the effects of reoperations due to inadequate treatment in DTCs on morbidity, mortality and costs were compiled and evaluated in our study.

According to the results obtained in a study by Scheller et al. [3], it was reported that molecular analyzes such as somatic mutations, gene expression profiles and miRNA tests should be performed while risk stratification is performed to decide on the type of surgery to be performed in DTCs.

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In DTC cases, recurrence occurs in approximately 15% of cases after the first operation. The most important risk factor leading to this is the aggressive nature of tumor cells [4].

Nieto et al. [5] detected 128 potential biomarkers for relapse in DTCs in a study they conducted, and they formed a 5-gene risk score as an independent prognostic predictive factor from these biomarkers. In a study by Harries et al. [6], it was reported that HUMARA and BRAF mutations, recurrence and lymph node metastasis rates are high in bilateral cancer (BC) and multifocal (MF) DTCs. In a single center study by Shaunak et al. [7], 478 DTC cases were analyzed and MF was reported to be an important risk factor. In a study by Kaliszevsky et al. [8], 27.1% of 177 PTC cases were found to be MF and 8.5% were BC. In a study conducted by Shen et al. [9], 33.3% of 110 patients who underwent reoperation had MF, 56.7% had BC DTC, complications of up to 32.6% occurred in these cases after reoperation, and reoperations put the patient at psychological and physical risk, therefore, it has been reported that definitive operations in DTCs should be standardized and reoperations should be avoided.

In a study conducted by Wilson et al. [10], 32 of 362 thyroidectomy cases performed by a single surgeon in a single center were reoperated for recurrence (1) or persistent cancer (31), and serious complications such as permanent hypocalcemia, NLI paralysis, and bleeding occurred in 21.8% of these cases. Due to the high complication rates in reoperations, it has been reported that resection should be adequate in primary surgery for thyroid malignancies. According to the results of Araz et al.'s [11] study in 1014 T1N0 DTC cases; MF, BC, and tumor diameter >1 cm were reported to be negative prognostic factors.

In a study, it was reported that the most appropriate treatment method in DTCs in children is total thyroidectomy (TT) and regional removal of metastasized lymph nodes, and that prognostic information can be obtained by using molecular diagnostic methods and personalized chemotherapy can be performed in these cases [12]. In a study by Sakiz et al. [13], in 1409 DTC cases, cases with and without Hashimoto's thyroiditis (HT) were compared, and they reported that lymphovascular invasion and perineural invasion were more common in cases with HT and affected prognosis poorly. Therefore, definitive operations should be performed in DTC cases with HT.

According to a study by Ullman et al. [14], the most important reason for the increase in the number of thyroid cancers in recent years is overdiagnosis. In low-risk DTCs, surgical treatment should be personalized and the extent of the resection should be adjusted according to the patient.

Cancer cells doubling time (CDT) and dwelling time (DT) in DTCs are much longer than in many other types of cancer. For example, although CDT is only 103 days in some types of breast cancers [15], in DTCs it is at least several years. Therefore, the active follow-up period should be long in all DTC cases in postoperative period to detect recurrence cases. In a study by Oh et al. [16], 273 papillary thyroid cancer (PTC) cases were followed under active observation and CDT was investigated. CDT was found to be less than 5 years in approximately 1/3 of these cases (rapid CDT cases), and 1/3 of them were found to have CDT more than 5 years (slow CDT cases). 19% of rapid CDT cases were operated within 29 months of the onset of active observation. It has been determined that the average age of these cases is younger, and that regional lymph node metastases occur within an average of 2.2 months.

In a study by Giovanella et al. [17] in 1421 DTC cases, 20% of DTCs recurred, 10% of these cases died, and investigating the Tg doubling time (TgDT) had an effect on tumor recurrence, predicting response to treatment, and overall survival (OS).

Park et al. [18] reported that Tg and Tg/TSH ratios could rise independently of the disease although there was no recurrence in the 6-year follow-up period after lobectomy (LT) surgeries performed in 208 low-risk DTC cases. Therefore, the authors stated that the monitoring of serum Tg values in DTC cases undergoing LT cannot have a predictive role.

Recurrence and mortality were investigated for an average of 18.9 years in 466 DTC cases who underwent curative treatment between 1981 and 1991 by Dong et al. [19]. Only 1.5% of these cases were treated with RAI. Cancer specific mortality was found to be 2.7, 6.2, 8.6 in the 10^{th}, 20^{th} and 30^{th} years respectively.

In DTC cases, residual cancer focus may remain after surgery due to insufficient resection. In a study conducted by Freeman, it was reported that approximately 1/3 of DTC cases left residual cancer or relapsed, and the main treatment method in these cases was reoperation [20]. In a study by Harries et al. [21], the effects of the type of surgery on mortality and morbidity were investigated in 849 DTC cases, 619 of which were unifocal and 230 (27.1%) of MF. According to the results obtained in the study, it was reported that LT did not increase mortality in selected MF cases. However, the mean follow-up period of the patients was found to be only 58 months in the study. In a study conducted by Bates et al. [22], in 69 DTC cases that underwent 92 reoperations, it was determined that 51% of the cases had MF, the mean reoperation time was 21 months, and the mean tumor diameter was 24 mm. It has been shown that the vast majority (97.1%) of the reoperated cases were not relapsed only residual.

In a study conducted by Biliomoria et al. [23] in 52,173 DTC cases, it was determined that the extent of the operation performed in >1cm DTC cases was directly parallel to the survival and did not affect cases with <1cm. However, the cases were followed only for an average of 10 years in this study. Considering the length of CDT in DTC cases, there is a possibility of increased mortality in DTC cases <1 cm when the active surveillance period is extended [18, 24].

In a study conducted in 1503 DTC cases followed with a standardized protocol, cancer-specific survival (CSS) was found to be 98.6%, 94.7%, and 87.4% at the 5^{th}, 10^{th}, and 15^{th} years, respectively. It was determined that 22.9% of the cases were MF, and tumor tissue was left behind in 24.6% of the cases after the operation, and the cancer-specific mortality (CSM) was higher in these cases. For this reason, it has been reported that the primary surgery should be exactly arranged in DTC cases [25]. In a study by Benkhaodura et al. [26], complication rates in ipsilateral and contralateral operations were compared in 73 patients, most of whom underwent reoperation due to inadequate thyroidectomy. In addition, it has been reported that complication rates are higher in ipsilateral reoperations, but the morbidity seen in contralateral reoperation cases is higher than in primary thyroidectomies, therefore, primary surgery should be performed adequately. Colombo et al. [27] compared the cases who underwent LT and TT in 370 low and intermediate risk DTC cases operated in a single center, and it was reported that 15% of the low risk DTCs who underwent LT and 50% of the cases in the intermediate risk group required additional treatment. In a study conducted by Medas et al. [28], 4420 DTC cases and 152 cases that were reoperated for recurrence after the primary operation were compared, and it was reported that LT was performed in 40.8% of the reoperated cases. It was found that the operation time, transient NLI paralysis, and permanent and transient hypoparathyroidism were significantly higher in patients who underwent reoperation. In a study by Young et al. [29], mortality was investigated in 222 patients who underwent reoperation in 11.986 >1cm DTC cases. Most of the reoperated cases have persistent disease and that the mortality due to the disease was independently statistically significantly higher in these patients. In a study conducted by Yim, recurrence occurred in 139 (10.2%) of 1357 DTC cases who underwent primary surgery by the same surgeon, within an average of 2.3 (1-10) years. It has been reported that TT was performed in only 2 of the relapsed cases, the mean tumor diameter was 2.5 cm, and 12.2% of them were T1N0 [30]. According to the results of a meta-analysis conducted by Bojoga et al. [31] in studies consisting of multiple cases, OS does not change statistically significantly compared to TT in conservative surgeries performed in selected low-risk DTC cases. However, the variables in this study show great heterogeneity and the follow-up period is less than 10 years in most of the cases.

Another dilemma among the authors in the treatment of DTCs is whether or not to use TSH suppression. One of the most important reasons for surgeons recommending conservative surgery in cases of low and intermediate DTC is that the patient does not use levothyroxine in the postoperative period. Also some authors have reported that TSH suppression does not prolong survival and leads to some complications such as osteoporosis [32]. However, some authors disagree on this respect: In a study conducted by Carhill et al. [33] in 4941 DTC cases, it was shown that moderate TSH suppression in the

early period at all stages prolongs OS. In a study conducted by Petersen et al. [34], on 1462 middle-aged women using levothyroxine for a long time, it was revealed that levothyroxine did not increase morbidity and mortality, and did not decrease the quality of life.

One of the most important reasons of the authors recommending LT as a surgical treatment method in DTCs is the higher complication rates of TT compared to LT. However, according to many authors, the most important factor affecting the complication rates in thyroid surgery is the high or low volume thyroid surgeon, rather than the extent of the operation. In a study conducted by Kandil et al. [35] in 46.261 cases, complication rates in thyroidectomy cases, regardless of the extent of the operation, are much lower in high-volume surgeons than in low-volume surgeons. When thyroidectomy operations are performed by high-volume surgeons, morbidity is low and minor complications can be easily treated [36].

Currently, surgery to remove the other lobe some time after primary LT in thyroid surgery has been simplified and defined as the second stage of an operation and called “complementary thyroidectomy” (CT). However, this application is actually a reoperation due to inadequate primary surgery.

It has been reported that CT should be performed in more than half of DTC cases [37] who underwent LT in accordance with ATA recommendations, based on the results of histopathological examinations performed during or after the operation [38, 39]. DiMarco et al. [40] reclassified 275 DTC cases who were in the low risk group and underwent LT preoperatively in accordance with ATA recommendations, according to operative and histopathological findings. Angioinvasion and local invasion or both were detected in 43.5% of these cases (117 cases), and accordingly CT was performed. In these cases, sex, age, familial anamnesis and tumor size were not found to be independent predictive factors.

Reoperations due to inadequate treatment in low and intermediate risk DTCs may have an increasing effect on total costs. In a study by Mammen and Cooper [41], it was reported that LT can be performed instead of TT in selected DTC cases, but they are not sure about the cost-effectiveness of these surgeries, and further research is needed on this subject. In a study conducted by Kim et al. [42] regarding the cost-effectiveness of treatments performed in DTC cases, TT was found to be the most cost-effective surgical method in terms of OS.

One of the most important problems in inadequate resections in DTC cases is the ineffectiveness of the treatment when RAI treatment is required, since thyroid tissue ablation is not performed. This situation also increases the total cost of treatment. In a study conducted in Germany, the cost of one session in the treatment of IUDs in thyroid diseases was found to be 1530 Euros on average [43].

According to the results we obtained in our study, performing reoperations due to inadequate treatment in low and intermediate risk DTC cases increases morbidity, mortality and costs. Therefore, operations such as TT or near TT should be preferred in all DTC cases. A second advantage of these operations is that thyroid ablation is easier when RAI treatment is required, and the treatment is more effective.

Moderate TSH suppression after the operation does not cause complications such as osteoporosis, and reduces the rates of recurrence and mortality.

Since CDT is long in low and intermediate risk DTC cases, it may take a very long time to detect residual tumor foci or recurrences. For this reason, the active follow-up period should be kept as long as 30 years, especially in cases where conservative operations were performed.

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Authors' contributions to the article

H.A. constructed the main idea and hypothesis of the study. A.A. developed the theory and arranged/edited the material and method section. H.A. has done the evaluation of the data in the Results section. H.A. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.