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핵의학적 관점에서 본 미국갑상선학회 진료권고안

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ATA Guideline in a View Point of Nuclear Medicine

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Since the American Thyroid Association's guidelines for the management of thyroid nodule and differentiated thyroid cancer were published in 1996 and revised in 2006 and 2009, significant scientific advances have occurred in the field. The new revised guideline for informing clinicians, patients, researchers, and health policy makers on updated published evidence relating to the diagnosis and management of thyroid nodules and differentiated thyroid cancer is recently announced. We reviewed the part which is related the nuclear medical diagnosis and treatment in the new guideline and expected it will be made the new guideline for nuclear medicine physician based on the consensus among nuclear medicine physicians and the verification through further research.

Key Words: Thyroid nodule, Differentiated thyroid cancer, Guideline, Nuclear medicine

서 론

1996년에 미국갑상선학회(American Thyroid Association: ATA)에서 갑상선결절과 분화갑상선암이 있는 환자들을 위한 진료권고안이 처음 발표되었고, 2006년에 이어 2009년에 그 내용이 개정된 이후 새로운 진료권고안이 만들어졌다.[1-3] 지난 15-20년간 세계적으로 갑상선결절 및 암의 빈도가 증가하면서 많은 수의 갑상선암에 대한 임상연구 논문이 발표되었고 그에 따른 갑상선결절과 분화갑상선암의 진단과 치료에서 많은 발전이 있었지만, 여러 분야에서 임상적인 논란거리들 또한 대두되었다. 그런 문제점들을 반영하여 새로운 진료권고안이 필요하다는 필요성이 증가하여 이번에 새로운 진료권고안이 발표되었지만, 미국갑상선학회 내에서도 이견이 많았고, 특히 우리나라의 임상적인 의료나 문화적인 환경 등을 고려해볼 때 다소 이견을 낼만한 요소들이 있다는 점을 확인할 수 있었다.

대한핵의학회에서는 대한갑상선학회와 함께 대한갑상선학회 갑상선결절 및 암 진료권고안 개정안이나 갑상선암 방사성요오드 치료에 관한 환자 안내서 등을 발표하였으나,[4,5] 핵의학 부문의 특수성 등을 고려한 핵의학 전문의들을 위한 갑상선 환자 진료권고안이 필요하다는 점에 많은 이들이 공감해왔다. 이번에 개정된 진료권고안에서 동위원소 치료에 대한 내용 또한 많은 수정이 이루어져서 대한핵의학회 내의 갑상선연구회를 중심으로 우리나라 실정에 맞는 핵의학 전문의를 위한 갑상선 환자 진료권고안의 제정에 나서게 되었고, 그에 대한 준비 과정으로 이번에 개정된 미국갑상선학회의 진료권고안을 살펴보고, 핵의학적인 면에서 논란이 될만한 점들을 검토해보고자 한다.

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본 론

치료반응에 대한 평가

추적 기간 중 얻어지는 모든 임상적, 생화학적, 영상학적, 그리고 조직병리학적인 결과들은 환자의 치료에 대한 결과를 평가하고 임상적인 상태를 재분류하는 데 사용된다. 이런 재분류 체계는 초기 치료를 한 후의 분화갑상선암 환자들을 임상적으로 관리하는 데 매우 중요하게 사용될 수 있다. 치료 반응에 따른 4가지 분류를 하는 개념은 Tuttle 등[6,7]과 Vaisman 등[8]에 의해 서술되었는데, 임상적인 영향과 치료에 대한 반응을 우수한 치료반응, 생화학적 불완전 치료반응, 구조적 불완전 치료반응, 미결정 치료반응으로 분류하고 있다 (Table 1).

우수한 치료반응: 질환에 대한 임상적이나 생화학적 또는 구조적인 증거가 없는 경우

생화학적 불완전 치료반응: 병변이 국소화된 증거는 없으나 티로글로불린 수치의 이상이나 항 티로글로불린 항체의 증가가 있는 경우

구조적 불완전 치료반응: 국소적 또는 원격전이가 지속되거나 새로 발견된 경우

미결정 치료반응: 확실하게 양성이나 악성으로 분류할 수가 없는 비특이적인 생화학적 또는 구조적 증상이 있는 경우로 명백한 구조적 병변의 증거가 없이 항 티로글로불린 항체가 안정적이거나 감소하는 환자들도 포함된다.

동위원소 치료 시행에 대한 권고

갑상선전절제 이후 잔여조직 제거를 위한 동위원소 치료는 분화갑상선암의 저위험군 환자에게는 권고되지 않는다.[9-19] 또한 엽절제를 한 경우나 전절제를 한 단발성의 미세유두암 환자에서 다른 나쁜 조건들이 없다면 잔여조직 제거를 위한 동위원소 치료는 권고되지 않는다. 전절제를 한 다발성의 미세유두암 환자에서도 다른 나쁜 조건들이 없다면 잔여조직 제거를 위한 동위원소 치료는 권고되지 않는다. 갑상선전절제를 시행한 분화갑상선암의 중간 위험군 환자에서는 동위원소 치료가 권고된다. 갑상선전절제를 시행한 분화갑상선암의 고위험군 환자에서는 잔여조직 제거를 위한 동위원소 치료가 강력하게 권고된다(Table 2).[20-23]

인체재조합 갑상선자극호르몬

인체재조합 갑상선자극호르몬을 사용하는 경우 잔여조직 제거의 효율을 낮추지 않으면서 단기간의 삶의 질을 높일 수 있고, 장기간의 추적관찰 결과에서도 의미 있는 차이를 보여주지 않아서, 광범위한 림프절 전이가 관찰되지 않는 저위험군과 중간위험군 분화갑상선암 환자들(예: T1-T3, N0/Nx/N1a, M0)에서 잔여조직 제거를 위한 동위원소 치료가 계획되어 있다면, 갑상선호르몬을 중단하는 대신에 인체재조합 갑상선자극호르몬을 사용한 준비과정으로 충분히 대체할 수 있다고 권고하고 있다. 원격전이는 없으나 광범위한 림프절 전이가 관찰되는 중간위험군의 분화갑상선암 환자에서도 동위원소 치료에 앞선 갑상선호르몬의 중단을 인체재조합 갑상선자극호르몬을 사용한 준비과정으로 대체할 수 있다고 권고하고 있다.[24-37]

고위험군 분화갑상선암 환자에서는 장기추적 관찰 결과에 대한 연구자료들이 충분하지 않아 동위원소 치료 전에 인체재조합 갑상선자극호르몬의 사용은 권고되고 있지 않다.[38-40] 다만, 동위원소 투여 이전의 갑상선호르몬 중단을 불가능하게 만들 수 있는 중요한 동반질환이 있는 분화갑상선암 환자들에서는 위험도와 관계없이 인체재조합 갑상선자극호르몬이 고려되어야 한다고 권고했다.

동위원소 치료용량의 결정

갑상선전절제를 시행한 저위험군 또는 저위험의 양상을 보이는 중간위험군의 갑상선암 환자에서 잔여조직 제거를 위한 동위원소 치료를 시행할 때는 고용량보다는 약 30 mCi (1.11 GBq)의 저용량 사용을 강하게 권고하고 있다.[41-48] 중간위험군이나 고위험군 환자에서 원격전이는 없으나 현미경적으로 병변이 발견되거나 의심되어 동위원소로 초기치료를 할 경우에는 30-150 mCi의 용량을 권고하고 있고, 그 이상의 용량을 사용하는 것이 재발병변을 더 감소시키지는 못하는 것으로 보고하고 있다.[49-52]

국소전이나 원격전이가 있는 환자에서 경험적인 동위원소 치료를 권고하고 있으나, 150 mCi 이상의 동위원소를 투여하는 경우에는 조직 내로의 최고 허용용량을 넘는 경우가 종종 발생하므로 70세가 넘는 환자에서는 허용하지 않도록 권고하고 있다.[53-55] 폐 전이나 골 전이가 있는 환자에서는 경험적으로 100-200 mCi (70세 이상에서는 100-150 mCi) 또는 선량측정계로 계산하여 투여 후 48시간에 전신에 80 mCi가 남도록 하

Table 1. Clinical implications of response to therapy re-classification in differentiated thyroid cancer patients treated with total thyroidectomy and RAI remnant ablation

Category	Definitions	Clinical outcomes	Management implications
Excellent response	Negative imaging and either Suppressed Tg<0.2 ng/mL* or TSH stimulated Tg<1 ng/mL*	1-4% recurrence <1% disease specific death	An excellent response to therapy should lead to an early decrease in the intensity and frequency of follow up and the degree of TSH suppression
Biochemical incomplete response	Negative imaging and Suppressed Tg>1 ng/mL* or Stimulated Tg>10 ng/mL* or Rising anti-Tg Ab levels	At least 30% spontaneously evolve to NED 20% achieve NED after additional therapy 20% develop structural disease <1% disease specific death	If associated with stable or declining serum Tg values, a biochemical incomplete response should lead to continued observation with ongoing TSH suppression in most patients. Rising Tg or Tg antibody values should prompt additional investigations and potentially additional therapies.
Structural incomplete response	Structural or functional evidence of disease With any Tg level +/- Tg Ab	50-85% continue to have persistent disease despite additional therapy Disease specific death rates as high as 11% with loco-regional metastases and 50% with structural distant metastases	A structural incomplete response may lead to additional treatments or ongoing observation depending on multiple clinico-pathologic factors including the size, location, rate of growth, RAI avidity, FDG avidity, and specific pathology of the structural lesions.
Indeterminate response	Non-specific findings on imaging studies Faint uptake in thyroid bed on RAI scanning Non-stimulated Tg detectable, but less than 1 ng/mL Stimulated Tg detectable, but less than 10 ng/mL or Tgantibodies stable or declining in the absence of structural or functional disease	15-20% will have structural disease identified during follow-up In the remainder, the non-specific changes are either stable, or resolve <1% disease specific death	An indeterminate response should lead to continued observation with appropriate serial imaging of the non-specific lesions and serum Tg monitoring. Non-specific findings that become suspicious over time can be further evaluated with additional imaging or biopsy.

*In the absence of anti-Tg antibodies

FDG: flourodeoxyglucose, RAI: radioactive Iodine, Tg: thyroglobulin, Tg Ab: thyroglobulin antibody, TSH: thyroid stimulating hormone

Table 2. Characteristics according to the ATA risk stratification system and AJCC/TNM staging system that may impact post-operative RAI decision-making

ATA recurrence risk Staging T N M	Description	Body of evidence suggests RAI improves disease-specific survival?	Body of evidence suggests RAI improves disease-free survival?	Post-surgical RAI indicated?
ATA low risk T1a N0, Nx M0, Mx	Tumor size ≤1 cm (uni-or multi-focal)	No	No	No
ATA low risk T1b, T2 N0, Nx M0, Mx	Tumor size >1-4 cm	No	Conflicting observational data	Not routine - May be considered for patients with aggressive histology or vascular invasion (ATA intermediate risk)
ATA low to intermediate risk T3 N0, Nx M0, Mx	Tumor size >4 cm	Conflicting data	Conflicting observational data	Consider - Need to consider presence of other adverse features. Advancing age may favor RAI use in some cases, but specific age and tumor size cut-offs subject to some uncertainty
ATA low to intermediate risk T3 N0, Nx M0, Mx	Microscopic extra-thyroidal extension, any tumor size	No	Conflicting observational data	Consider - Generally favored based on risk of recurrent disease. Smaller tumors with microscopic ETE may not require RAI
ATA low to intermediate risk T1-3 N1a M0, Mx	Central compartment neck lymph node metastases	No, except possibly in subgroup of patients ≥45 years of age (NTCTCSG stage III)	Conflicting observational data	Consider - Generally favored, due to somewhat higher risk of persistent or recurrent disease, especially with increasing number of large (>2-3 cm) or clinically evident lymph nodes or presence of extra-nodal extension. Advancing age may also favor RAI use. However, there is insufficient data to mandate RAI use in patients with few (<5) microscopic nodal metastases in central compartment in absence of other adverse features.
ATA low to intermediate risk T1-3 N1b M0, Mx	Lateral neck or mediastinal lymph node metastases	No, except possibly in subgroup of patients ≥45 years of age	Conflicting observational data	Consider - Generally favored, due to higher risk of persistent or recurrent disease, especially with increasing number of macroscopic or clinically evident lymph nodes or presence of extra-nodal extension. Advancing age may also favor RAI use
ATA high risk T4 Any N Any M	Any size, gross extrathyroidal extension	Yes (observational data)	Yes (observational data for disease persistence and recurrence)	Yes
ATA high risk M1 Any T Any N	Distant metastases	Yes (observational data)	Yes (observational data)	Yes

AJCC: American Joint Committee on Cancer, ATA: American Thyroid Association, NTCTCSG: National Thyroid Cancer Treatment Cooperative Study Group, RAI: radioactive Iodine, TNM: tumor node metastasis

거나, 적색골수에 200 cGy가 되도록 투여하도록 권고하고 있다.[56-59]

방사성요오드 저항성 분화갑상선암

방사성요오드 저항성 분화갑상선암은 종양세포나 전이세포가 방사성요오드를 축적하지 않아서 처음 진단 시나 치료 후 전신스캔에서 갑상선 자리 주위에 섭취가 없는 경우, 이전에 방사성요오드 섭취가 관찰되었으나 종양세포가 방사성요오드를 축적하는 능력을 상실한 경우, 방사성요오드가 어떤 병변에서는 축적되나 다른 병변에서는 축적되지 않는 경우, 그리고 의미있는 방사성요오드의 축적이 관찰됨에도 전이병변이 진행되는 경우로 정의하였다.[60] 방사성요오드에 저항성이 있는 분화갑상선암을 가진 환자에서는 더 이상의 방사성요오드 치료는 권고하지 않았다.

Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

FDG-PET 검사는 갑상선결절의 미세침흡인생검의 세포학적인 검사결과가 불충분할 때 권고될 수 있는 영상검사라는 데는 동의하지 않았으나,[61-63] FDG-PET-CT 검사에서 갑상선결절의 국소적인 섭취가 관찰될 때는 약 35% 정도까지 악성종양이 발생될 가능성이 있어 미세침흡인생검이 필요함을 강하게 권고하고 있다.[64-66] 또한 갑상선암의 수술 전에 필수적으로 시행되어야 할 검사로는 권고하지 않았으나, FDG-PET 검사가 목과 종격동 전이, 그리고 원격전이를 진단하는 데 있어서 민감도가 높은 검사임에는 동의하고 있다.

FDG-PET 검사는 저분화성 갑상선암이나 허슬세포암의 초기 병기설정이나, 전이 병소를 찾거나 고위험도 환자를 위한 예후평가를 위해서, 전이 등에 대한 국소 또는 전신치료의 치료반응 평가를 위해서 필요하다고 권고하고 있다.[67,68]

Single-Photon Emission Computerized Tomography (SPECT-CT)

갑상선호르몬 중단 후의 진단영상 또는 동위원소 치료 후 전신영상에서 SPECT-CT를 사용한 검사가 전신스캔에 의한 평면영상보다 더 나은 해부학적인 위치를 알려주고, 재발이나 전이 소견과 비특이적인 섭취 소견을 감별하는 데 더 많은 정보를 제공한다는 점에 동의하고 SPECT-CT에 의한 검사를 권고하고 있다.[69-79]

결 론

갑상선결절과 분화갑상선암에 대한 미국갑상선학회의 새로운 진료권고안의 내용 중 핵의학적 진단과 치료에 밀접한 관련이 있는 부분들을 살펴보았다. 이 중 치료반응에 대한 새로운 평가방법이나 인체재조합 갑상선자극호르몬의 시행, 방사성요오드 저항성 분화갑상선암에 관련된 내용은 그동안의 많은 연구와 지식이 축적됨에 따른 결과물로 여겨지고 있어 핵의학적인 측면에서도 충분히 수용 가능할 것으로 여겨지고 있고, 특히나 FDG-PET과 SPECT-CT와 관련된 내용들이 진료권고안에 포함된 것은 충분히 고무적인 일로 받아들여지고 있다.

다만, 핵의학적인 측면에서 기존의 권고안과 상당히 다른 내용들이 포함되어 있는 동위원소 치료 시행에 대한 권고와 동위원소 치료용량의 결정에 관련된 내용들은 대한핵의학회 내에서도 찬반이 엇갈리고 있고, 우리나라와 같이 평상시 요오드 섭취가 많은 지역에서 사용되는 동위원소 치료용량은 그렇지 않은 지역과는 확실한 차이가 있을 것이라는 반론들이 제시되고 있다. 따라서 미국갑상선학회의 새로운 진료권고안에 대한 내용들을 바탕으로 하여 향후 대한핵의학회 내의 갑상선연구회를 중심으로 여러 논의 과정을 거치고 수정 보완하여 핵의학전문의를 위한 갑상선암의 진료권고안이 제정될 것으로 예상된다. 그러나 동위원소 치료를 포함한 여러 부분에서 향후의 추가 연구를 통한 검증과 핵의학 전문의들 내의 합의가 필요할 것으로 생각된다.

중심 단어: 갑상선결절, 분화갑상선암, 방사성요오드 치료.

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