# Supplementary Material 1. Quality of literature and evidence level, and grades of recommendations

# A. Preoperative workup

**A1. Which test is helpful to evaluate the extent of the primary tumor in patients with locally invasive DTC for surgery?**

**Recommendation 1.**

Routine preoperative evaluation of vocal fold movements or laryngeal structures using laryngoscopy is recommended to determine the extent of disease in patients with locally invasive DTC.

(Strong recommendation/low-quality evidence)

**Recommendation 1.**

Routine preoperative evaluation of vocal fold movements or laryngeal structures using laryngoscopy is recommended to determine the extent of disease in patients with locally invasive DTC.

**(Strong recommendation/low-quality evidence)**

* **Final included studies**

|  |  |
| --- | --- |
| Study number | Included studies |
| Non-RCT 2 | A novel lateral-approach laryngeal ultrasonography for vocal cord evaluation. Surgery. 2016 Jan;159(1):52-6. |
| Non-RCT 5 | The importance of preoperative laryngoscopy in patients undergoing thyroidectomy: voice, vocal cord function, and the preoperative detection of invasive thyroid malignancy. Surgery. 2006 Mar;139(3):357-62. |
| Non-RCT 7 | Using MR imaging to predict invasion of the recurrent laryngeal nerve by thyroid carcinoma. AJR Am J Roentgenol. 2003 Mar;180(3):837-42.  |

* **Risk of bias**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study number | The firstauthor (year) | Comparability of participants | Selectionof participants | Confounding | Measurementof intervention | Blinding of outcomeassessment | Measurementof outcomes | IncompleteOutcome data | Selectivereporting | Funding |
| Non-RCT 2 | JW Woo (2016) |  |  |  |  |  |  |  |  |  |
| Non-RCT 5 | GW Randolph (2006) |  |  |  |  |  |  |  |  |  |
| Non-RCT 7 | S Takashima (2003) |  |  |  |  |  |  |  |  |  |

 Low risk of bias;  Unclear risk of bias; : High risk of bias

* **Levels of evidence**

|  |  |
| --- | --- |
|  | No (0), Serious (–1), Very serious (–2) |
| Study design | No. of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Publicationbias | Quality of evidence | Importance |
| RCT |  |  |  |  |  |  |  |  |
| Non-RCT | 3 | –1 | 0 | –1 | 0 | 0 | Low | 6 |

RCT, randomized controlled trials.

* **Strength of recommendation**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Balance of benefits & harms | O |  |
| Quality of evidence | Low |  |
| Values and preferences of patients | O |  |
| Resource use (Cost) |  | O |
| Acceptability of recommendation | Yes | No |
| O |  |
| Level of recommendation | Strong | Conditional |
| O |  |

**Recommendation 2**

Preoperative evaluation of the primary tumor using ultrasonography is recommended in patients undergoing thyroid surgery for locally invasive DTC.

(Strongrecommendation/moderate-quality evidence)

**Recommendation 2**

Preoperative evaluation of the primary tumor using ultrasonography is recommended in patients undergoing thyroid surgery for locally invasive DTC.

**(Strong recommendation/moderate-quality evidence)**

* **Final included studies**

|  |  |
| --- | --- |
| Study number | Included studies |
| Non-RCT 1 | Ultrasonographic features associated with false-negative and false-positive results of extrathyroidal extensions in papillary thyroid microcarcinoma. Eur Arch Otorhinolaryngol. 2018 Nov;275(11):2817-2822. |
| Non-RCT 3 | Ultrasound assessment of degrees of extrathyroidal extension in papillary thyroid microcarcinoma. Endocr Pract. 2014 Oct;20(10):1037-43.  |
| Non-RCT 6 | Ultrasonography as a method of screening for tracheal invasion by papillary thyroid cancer. Surg Today. 2005;35(10):819-22. |
| Non-RCT 10 | Staging papillary carcinoma of the thyroid: magnetic resonance imaging vs ultrasound of the neck. Clin Radiol. 2000 Mar;55(3):222-6. |
| Non-RCT 12 | Preoperative staging of thyroid papillary carcinoma with ultrasonography. Eur J Radiol. 1998 Nov;29(1):4-10.   |

* **Risk of bias**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstauthor (year) | Comparability of participants | Selectionof participants | Confounding | Measurement of intervention | Blinding of outcomeassessment | Measurementof outcomes | IncompleteOutcome data | Selectivereporting | Funding |
| Non-RCT 1 | YC Lee (2018) |  |  |  |  |  |  |  |  |  |
| Non-RCT 3 | SJ Moon (2014) |  |  |  |  |  |  |  |  |  |
| Non-RCT 6 | Tomoda C (2005) |  |  |  |  |  |  |  |  |  |
| Non-RCT 10 | AD King (2000) |  |  |  |  |  |  |  |  |  |
| Non-RCT 12 | K Shimamoto (1998) |  |  |  |  |  |  |  |  |  |

* **Levels of evidence**

|  |  |
| --- | --- |
|  | No (0), Serious (-1), Very serious (-2) |
| Study design | No. of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Publicationbias | Quality of evidence | Importance |
| RCT |  |  |  |  |  |  |  |  |
| Non-RCT | 5 | 0 | 0 | 0 | 0 | 0 | Moderate | 7 |

* **Strength of recommendation**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Balance of benefits & harms  | O |  |
| Quality of evidence | Moderate |  |
| Values and preferences of patients | O |  |
| Resource use (Cost) | O |  |
| Acceptability of recommendation | Yes | No |
| O |  |
| Level of recommendation | Strong | Conditional |
| O |  |

**Recommendation 3**

Cross-sectional imaging (computed tomography or magnetic resonance imaging) is helpful for evaluating anatomical relationships between the tumor and surrounding visceral structures in locally invasive DTC.

(Strong recommendation/low-quality evidence)

* **Final included studies**

|  |  |
| --- | --- |
| Study number | Included studies |
| Non-RCT 4 | Locally advanced thyroid cancer: can CT help in prediction of extrathyroidal invasion to adjacent structures.  AJR Am J Roentgenol. 2010 Sep;195(3):W240-4. |
| Non-RCT 7 | Using MR imaging to predict invasion of the recurrent laryngeal nerve by thyroid carcinoma. AJR Am J Roentgenol. 2003 Mar;180(3):837-42.  |
| Non-RCT 11 | Differentiated thyroid carcinomas. Prediction of tumor invasion with MR imaging. Acta Radiol. 2000 Jul;41(4):377-83 |

* **Risk of bias**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstauthor (year) | Comparability of participants | Selectionof participants | Confounding | Measurementof intervention | Blinding of outcomeassessment | Measurementof outcomes | IncompleteOutcome data | Selectivereporting | Funding |
| Non-RCT 4 | YL Seo (2010) |  |  |  |  |  |  |  |  |  |
| Non-RCT 7 | S Takashima (2003) |  |  |  |  |  |  |  |  |  |
| Non-RCT 11 | S Takashima (2000) |  |  |  |  |  |  |  |  |  |

* **Levels of evidence**

|  |  |
| --- | --- |
|  | No (0), Serious (–1), Very serious (–2) |
| Study design | No. of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Publicationbias | Quality of evidence | Importance |
| RCT |  |  |  |  |  |  |  |  |
| Non-RCT | 3 | –1 | 0 | 0 | 0 | 0 | Low | 6 |

* **Strength of recommendation**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Balance of benefits & harms  | O |  |
| Quality of evidence | Low |  |
| Values and preferences of patients | O |  |
| Resource use (Cost) | O |  |
| Acceptability of recommendation | Yes | No |
| O |  |
| Level of recommendation | Strong | Conditional |
| O |  |

**Recommendation 4**

Bronchoscopy/esophagoscopy evaluation may provide ancillary information about the extent of disease in patients with suspected tracheal or esophageal invasion.

(Conditional recommendation/low-quality evidence)

* **Final included studies**

|  |  |
| --- | --- |
| Study number | Included studies |
| Non-RCT 8 | Endoscopic ultrasonography in patients with thyroid cancer: its usefulness and limitations for evaluating esophagopharyngeal invasion. Endoscopy. 2002 Jun;34(6):457-60. |
| Non-RCT 9 | Bronchoscopic diagnosis of thyroid cancer with laryngotracheal invasion.Arch Surg. 2001 Oct;136(10):1185-9. |

* **Risk of bias**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstauthor (year) | Comparability of participants | Selectionof participants | Confounding | Measurementof intervention | Blinding of outcomeassessment | Measurementof outcomes | IncompleteOutcome data | Selectivereporting | Funding |
| Non-RCT 8 | E Koike (2002) |  |  |  |  |  |  |  |  |  |
| Non-RCT 9 | E Koike (2001) |  |  |  |  |  |  |  |  |  |

* **Levels of evidence**

|  |  |
| --- | --- |
|  | No (0), Serious (–1), Very serious (–2) |
| Study design | No. of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Publicationbias | Quality of evidence | Importance |
| RCT |  |  |  |  |  |  |  |  |
| Non-RCT | 2 | –1 | 0 | 0 | 0 | –1 | Low | 0 |

* **Strength of recommendation**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Balance of benefits & harms  | O |  |
| Quality of evidence | Low |  |
| Values and preferences of patients | O |  |
| Resource use (Cost) | O |  |
| Acceptability of recommendation | Yes | No |
| O |  |
| Level of recommendation | Strong | Conditional |
|  | O |

**A2. What is the role of preoperative workup in patients with thyroid cancer with neck metastasis?**

**Recommendation 5**

Diagnostic neck US should be performed in patients diagnosed with locally invasive thyroid cancer for detection of central or lateral neck metastasis.

(Strong recommendation/moderate-quality evidence)

* **Final included studies**

|  |  |
| --- | --- |
| Study number | Included studies |
| Meta-analysis 1 | Meta-analysis of ultrasound for cervical lymph nodes in papillary thyroid cancer: Diagnosis of central and lateral compartment nodal metastases. Eur J Radiol. 2019 Mar;112:14-21.  |
| Non-RCT 1 | Staging of papillary thyroid carcinoma with ultrasonography: performance in a large series. Ann Surg Oncol. 2011 Dec;18(13):3572-8 |
| Non-RCT 2 | Efficacy of preoperative neck ultrasound in the detection of cervical lymph node metastasis from thyroid cancer. 2011 Mar;121(3):487-91. |
| Non-RCT 3 | Ultrasonographic differentiation between metastatic and benign lymph nodes in patients with papillary thyroid carcinoma. J Ultrasound Med. 2005 Oct;24(10):1385-9.  |
| Non-RCT 4 | Pre-operative ultrasound diagnosis of nodal metastasis in papillary thyroid carcinoma patients according to nodal compartment. Ultrasound Med Biol. 2015 May;41(5):1294-300. |

* **Risk of bias**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstAuthor (year) | Was an a priori design provided? | Was there dupicate study selection and data extraction? | Was a comprehensive literature search performed? | Was the status of publicatoin usea as an inclusion criterion? | List of included and exclude study | Were the characteristics of the included studies provided? | Was the scientific quality of the include studies assessed and documented? | Were the methods used to combine the findings of studies appropriate? | Publication bias assessed and discussed | Potential sources of conflict of interest |
| Meta-analysis 1 | Zhao (2019) | Yes | ? | Yes | Yes | Yes | Yes | ? | ? | No | Yes |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstauthor (year) | Comparability of participants | Selectionof participants | Confounding | Measurementof intervention | Blinding of outcomeassessment | Measurementof outcomes | IncompleteOutcome data | Selectivereporting | Funding |
| Non-RCT 1 | Hwang (2011) |  |  |  |  |  |  |  |  |  |
| Non-RCT 2 | Choi (2011) |  |  |  |  |  |  |  |  |  |
| Non-RCT 3 | Rosário (2005) |  |  |  |  |  |  |  |  |  |
| Non-RCT 4 | Lee (2015)  |  |  |  |  |  |  |  |  |  |

* **Levels of evidence**

|  |  |
| --- | --- |
|  | No (0), Serious (-1), Very serious (-2) |
| Study design | No. of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Publicationbias | Quality of evidence | Importance |
| RCT | 1 | 0 | 0 | 0 | 0 | 0 | Moderate | 9 |
| Non-RCT | 4 | 0 | 0 | 0 | 0 | 0 | Moderate | 9 |

* **Strength of recommendation**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Balance of benefits & harms  | O |  |
| Quality of evidence |  | O |
| Values and preferences of patients | O |  |
| Resource use (Cost) |  | O |
| Acceptability of recommendation | Yes | No |
| O |  |
| Level of recommendation | Strong | Conditional |
| O |  |

**Recommendation 6**

US-guided fine needle aspiration of suspicious lymph nodes should be considered to confirm the presence of metastasis.

(Conditional recommendation/moderate-quality evidence)

**Recommendation 7**

FNA-Tg may be useful to identify metastasis in selected cases with suspicious cervical lymph nodes. The combination of FNA cytology and FNA-Tg may show better diagnostic performance compared with cytology alone.

(Conditional recommendation/moderate-quality evidence)

* **Final included studies**

|  |  |
| --- | --- |
| Study number | Included studies |
| Meta-analysis 1 | Diagnostic value of cytology, thyroglobulin, and combination of them in fine-needle aspiration of metastatic lymph nodes in patients with differentiated thyroid cancer: A systematic review and network meta-analysis. Medicine (Baltimore). 2019 Nov;98(45):e17859.  |
| Meta-analysis 2 | Thyroglobulin in lymph node fine-needle aspiration washout: a systematic review and meta-analysis of diagnostic accuracy. J Clin Endocrinol Metab. 2014 Jun;99(6):1970-82. |
| Non-RCT 1 | Thyroglobulin measurements in washout of fine needle aspirates in cervical lymph nodes for detection of papillary thyroid cancer metastases.Arq Bras Endocrinol Metabol. 2010 Aug;54(6):550-4. |
| Non-RCT 2 | Cervical Lymph Node Fine-Needle Aspiration and Needle-Wash Thyroglobulin Reflex Test for Papillary Thyroid Carcinoma. Endocr Pathol. 2018 Dec;29(4):346-350.   |
| Non-RCT 3 | Diagnostic utility of thyroglobulin detection in fine-needle aspiration of cervical cystic metastatic lymph nodes from papillary thyroid cancer with negative cytology. Thyroid. 2003 Dec;13(12):1163-7.  |
| Non-RCT 4 | Lymph node fine-needle aspiration washout thyroglobulin in papillary thyroid cancer: Diagnostic value and the effect of thyroglobulin antibodies. Endocr Res. 2016 Nov;41(4):281-289.  |

* **Risk of bias**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstAuthor (year) | Was an a priori design provided? | Was there dupicate study selection and data extraction? | Was a comprehensive literature search performed? | Was the status of publicatoin usea as an inclusion criterion? | List of included and exclude study | Were the characteristics of the included studies provided? | Was the scientific quality of the include studies assessed and documented? | Were the methods used to combine the findings of studies appropriate? | Publication bias assessed and discussed | Potential sources of conflict of interest |
| Meta-analysis 1 | Y Xu (2019) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | ? | Yes | Yes |
| Meta-analysis 2 | G Grani(2014) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | ? | Yes | Yes |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstauthor (year) | Comparability of participants | Selectionof participants | Confounding | Measurementof intervention | Blinding of outcomeassessment | Measurementof outcomes | IncompleteOutcome data | Selectivereporting | Funding |
| Non-RCT 1 | Z Al (2016) |  |  |  |  |  |  |  |  |  |
| Non-RCT 2 | X Zhang (2018) |  |  |  |  |  |  |  |  |  |
| Non-RCT 3 | M Cignarelli (2003) |  |  |  |  |  |  |  |  |  |
| Non-RCT 4 | C. Degertekin (2016) |  |  |  |  |  |  |  |  |  |

* **Levels of evidence**

|  |  |
| --- | --- |
|  | No (0), Serious (-1), Very serious (-2) |
| Study design | No. of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Publicationbias | Quality of evidence | Importance |
| RCT | 2 | 0 | 0 | 0 | 0 | 0 | Moderate | 9 |
| Non-RCT | 4 | 0 | 0 | 0 | 0 | 0 | Moderate | 9 |

* **Strength of recommendation**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Balance of benefits & harms  | O |  |
| Quality of evidence |  | O |
| Values and preferences of patients | O |  |
| Resource use (Cost) |  | O |
| Acceptability of recommendation | Yes | No |
| O |  |
| Level of recommendation | Strong | Conditional |
|  | O |

**Recommendation 8**

CT with contrast enhancement is recommended to evaluate central and lateral metastatic lymph nodes in patients with locally invasive thyroid cancer.

(Strong recommendation/moderate-quality evidence)

* **Final included studies**

|  |  |
| --- | --- |
| Study number | Included studies |
| Meta-analysis 1 | Performance of CT in the Preoperative Diagnosis of Cervical Lymph Node Metastasis in Patients with Papillary Thyroid Cancer: A Systematic Review and Meta-Analysis. AJNR Am J Neuroradiol. 2017 Jan;38(1):154-161. |
| Non-RCT 1 | Clinical and imaging assessment of cervical lymph node metastasis in papillary thyroid carcinomas. World J Surg. 2010 Jul;34(7):1494-9. |
| Non-RCT 2 | Preoperative staging of papillary thyroid carcinoma: comparison of ultrasound imaging and CT. AJR Am J Roentgenol. 2009 Sep;193(3):871-8.  |
| Non-RCT 3 | Value of CT added to ultrasonography for the diagnosis of lymph node metastasis in patients with thyroid cancer. Head Neck. 2018 Oct;40(10):2137-2148.  |

* **Risk of bias**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstAuthor (year) | Was an a priori design provided? | Was there dupicate study selection and data extraction? | Was a comprehensive literature search performed? | Was the status of publicatoin usea as an inclusion criterion? | List of included and exclude study | Were the characteristics of the included studies provided? | Was the scientific quality of the include studies assessed and documented? | Were the methods used to combine the findings of studies appropriate? | Publication bias assessed and discussed | Potential sources of conflict of interest |
| Meta-analysis 1 | CH Suh (2017) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | ? | No | ? |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstauthor (year) | Comparability of participants | Selectionof participants | Confounding | Measurementof intervention | Blinding of outcomeassessment | Measurementof outcomes | IncompleteOutcome data | Selectivereporting | Funding |
| Non-RCT 1 | Y Lee (2017) |  |  |  |  |  |  |  |  |  |
| Non-RCT 2 | YJ Choi (2010) |  |  |  |  |  |  |  |  |  |
| Non-RCT 3 | JS Choi (2009) |  |  |  |  |  |  |  |  |  |

* **Levels of evidence**

|  |  |
| --- | --- |
|  | No (0), Serious (-1), Very serious (-2) |
| Study design | No. of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Publicationbias | Quality of evidence | Importance |
| RCT | 1 | 0 | 0 | 0 | 0 | 0 | Low | 8 |
| Non-RCT | 4 | -1 | 0 | 0 | 0 | 0 | Low | 8 |

* **Strength of recommendation**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Balance of benefits & harms  | O |  |
| Quality of evidence |  | O |
| Values and preferences of patients | O |  |
| Resource use (Cost) |  | O |
| Acceptability of recommendation | Yes | No |
| O |  |
| Level of recommendation | Strong | Conditional |
| O |  |

**Recommendation 9**

Preoperative 18FDG-PET or PET/CT may have a complementary role in detecting regional or distant metastasis in patients with advanced thyroid cancer.

(Conditional recommendation/low-quality evidence)

* **Final included studies**

|  |  |
| --- | --- |
| Study number | Included studies |
| Meta-analysis 1 | Diagnostic values of F-18 FDG PET or PET/CT, CT, and US for preoperative lymph node staging in thyroid cancer: A network meta-analysis.  Br J Radiol. 2021 Apr 1;94(1120):20201076. |
| Non-RCT 1 | The value of preoperative PET–CT in papillary thyroid cancer. J Int Med Res. 2013 Apr;41(2):445-56. |

* **Risk of bias**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstAuthor (year) | Was an a priori design provided? | Was there dupicate study selection and data extraction? | Was a comprehensive literature search performed? | Was the status of publicatoin usea as an inclusion criterion? | List of included and exclude study | Were the characteristics of the included studies provided? | Was the scientific quality of the include studies assessed and documented? | Were the methods used to combine the findings of studies appropriate? | Publication bias assessed and discussed | Potential sources of conflict of interest |
| Meta-analysis 1 | K Kim (2021) | Yes | ? | Yes | ? | Yes | Yes | Yes | ? | Yes | Yes |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstauthor (year) | Comparability of participants | Selectionof participants | Confounding | Measurementof intervention | Blinding of outcomeassessment | MeasurementOf outcomes | IncompleteOutcome data | Selectivereporting | Funding |
| Non-RCT 1 | BS Kim (2013) |  |  |  |  |  |  |  |  |  |

* **Levels of evidence**

|  |  |
| --- | --- |
|  | No (0), Serious (-1), Very serious (-2) |
| Study design | No. of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Publicationbias | Quality of evidence | Importance |
| RCT | 1 | 0 | 0 | 0 | 0 | 0 | Low | 6 |
| Non-RCT | 1 | -1 | 0 | -1 | 0 | 0 | Low | 6 |

* **Strength of recommendation**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Balance of benefits & harms  | O |  |
| Quality of evidence |  | O |
| Values and preferences of patients | O |  |
| Resource use (Cost) |  | O |
| Acceptability of recommendation | Yes |  No |
| O |  |
| Level of recommendation | Strong | Conditional |
|  | O |

1. **Surgical extent of thyroidectomy**

**B1. What is the appropriate surgical extent of thyroidectomy in T3/T4 thyroid cancer?**

**Recommendation 10.**

1. If the tumor size is ≥ 4 cm, (near) total thyroidectomy should be considered regardless of infiltration.

(Conditional recommendation/moderate-quality evidence)

1. If gross extrathyroidal extension invading the strap muscle exists in thyroid cancer, (near) total thyroidectomy could be considered.

(Conditional recommendation/moderate-quality evidence)

1. If gross extrathyroidal extension into major neck structures such as subcutaneous soft tissues, larynx, trachea, esophagus or recurrent laryngeal nerve, (near) total thyroidectomy should be considered.

(Conditional recommendation/low-quality evidence)

* **Final included studies**

|  |  |
| --- | --- |
| Study number | Included studies |
| Non-RCT 1 | The new T3b category has clinical significance? SEER-based study. Clinical Endocrinology 94(3): 449-459. |
| Non-RCT 2 | A Relook at the T Stage of Differentiated Thyroid Carcinoma with a Focus on Gross Extrathyroidal Extension. Thyroid 29(2): 202-208. |
| Non-RCT 3 | Prognostic significance of gross extrathyroidal extension invading only strap muscles in differentiated thyroid carcinoma. Br J Surg 105(9): 1155-1162. |
| Non-RCT 4 | Clinical Significance of Gross Invasion of Strap Muscles in Patients With 1- to 4-cm-Sized Papillary Thyroid Carcinoma Undergoing Lobectomy. Ann Surg Oncol 26(13): 4466-4471. |
| Non-RCT 5 | Extent of Extrathyroidal Extension as a Significant Predictor of Nodal Metastasis and Extranodal Extension in Patients with Papillary Thyroid Carcinoma. Ann Surg Oncol 24(2): 460-468. |
| Non-RCT 6 | Extrathyroidal extension predicts negative clinical outcomes in papillary thyroid cancer. Surgery 169(1): 2-6. |
| Non-RCT 7 | Extrathyroidal Extension: Does Strap Muscle Invasion Alone Influence Recurrence and Survival in Patients with Differentiated Thyroid Cancer? Ann Surg Oncol 25(11): 3380-3388. |
| Non-RCT 8 | Implications of Extrathyroidal Extension Invading Only the Strap Muscles in Papillary Thyroid Carcinomas. Thyroid 30(1): 57-64. |

* **Risk of bias**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstauthor (year) | Comparability of participants | Selectionof participants | Confounding | Measurementof intervention | Blinding of outcomeassessment | Measurementof outcomes | Incompleteoutcomedata | Selectivereporting | Funding |
| Non-RCT 1 | J. Xiang (2021) |  |  |  |  |  |  |  |  |  |
| Non-RCT 2 | E. Song (2019) |  |  |  |  |  |  |  |  |  |
| Non-RCT 3 | S. Y. Park (2018) |  |  |  |  |  |  |  |  |  |
| Non-RCT 4 | E. Song (2019) |  |  |  |  |  |  |  |  |  |
| Non-RCT 5 | Kim JW (2017) |  |  |  |  |  |  |  |  |  |
| Non-RCT 6 | MD Bortz (2021) |  |  |  |  |  |  |  |  |  |
| Non-RCT 7 | M. Amit (2018) |  |  |  |  |  |  |  |  |  |
| Non-RCT 8 | Li. G (2020) |  |  |  |  |  |  |  |  |  |

* **Levels of evidence**

|  |  |
| --- | --- |
|  | No (0), Serious (-1), Very serious (-2) |
| Study design | No. of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Publicationbias | Quality of evidence | Importance |
| RCT |  |  |  |  |  |  |  |  |
| Non-RCT | 8 | 0 | 0 | 0 | 0 | 0 | Moderate | 8 |

* **Strength of recommendation**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Balance of benefits & harms  | O |  |
| Quality of evidence |  | O |
| Values and preferences of patients | O |  |
| Resource use (Cost) |  | O |
| Acceptability of recommendation | Yes | No |
| O |  |
| Level of recommendation | Strong |  |
|  | O |

1. **Surgery for invasion into the strap muscles, RLN, laryngeal framework and esophagus**

**C1. What is the appropriate surgical margin in thyroid cancer with invasion into the strap muscles or soft tissue?**

**Recommendation 11**

If invasion of the strap muscles is confirmed by inspection or palpation with/without frozen biopsy during surgery, complete resection of the invaded tissue with adequate safety margins is recommended.

(Conditional recommendation/low-quality evidence)

* **Final included studies**

|  |  |
| --- | --- |
| Study number | Included studies |
| Non-RCT 1 | A Relook at the T Stage of Differentiated Thyroid Carcinoma with a Focus on Gross Extrathyroidal Extension. Thyroid 29(2): 202-208. |
| Non-RCT 2 | Extrathyroidal Extension: Does Strap Muscle Invasion Alone Influence Recurrence and Survival in Patients with Differentiated Thyroid Cancer? Ann Surg Oncol 25(11): 3380-3388. |
| Non-RCT 3 | Characteristics and significance of minimal and maximal extrathyroidal extension in papillary thyroid carcinoma. Oral Oncology 51(2015) 759-763 |
| Non-RCT 4 | Clinical Significance of Gross Invasion of Strap Muscles in Patients With 1- to 4-cm-Sized Papillary Thyroid Carcinoma Undergoing Lobectomy. Ann Surg Oncol 26(13): 4466-4471. |
| Non-RCT 5 | Extrathyroidal extension predicts negative clinical outcomes in papillary thyroid cancer. Surgery 169(1): 2-6. |
| Non-RCT 6 | Implications of Extrathyroidal Extension Invading Only the Strap Muscles in Papillary Thyroid Carcinomas. Thyroid 30(1): 57-64. |
| Non-RCT 7 | Occult invasion of sternothyroid muscle by differentiated thyroid cancer. European Archives of Oto-Rhino-Laryngology (2018) 275:233–238  |
| Non-RCT 8 | Microscopic positive margins strongly predict reduced disease-free survival in pT4a papillary thyroid cancer. Head & Neck. 2019;41:2549–2554. |
| Non-RCT 9 | The extent of extrathyroidal extension is a key determinant of prognosis in T4a papillary thyroid cancer? J Surg Oncol. 2019;120:1016–1022. |

* **Risk of bias**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstauthor (year) | Comparability of participants | Selectionof participants | Confounding | Measurement of intervention | Blinding of outcomeassessment | MeasurementOf outcomes | IncompleteOutcome data | Selectivereporting | Funding |
| Non-RCT 1 | E. Song (2019) |  |  |  |  |  |  |  |  |  |
| Non-RCT 2 | M. Amit (2018) |  |  |  |  |  |  |  |  |  |
| Non-RCT 3 | B. Jin (2015) |  |  |  |  |  |  |  |  |  |
| Non-RCT 4 | E. Song (2019) |  |  |  |  |  |  |  |  |  |
| Non-RCT 5 | Li G (2020) |  |  |  |  |  |  |  |  |  |
| Non-RCT 6 | Z Khan (2018) |  |  |  |  |  |  |  |  |  |
| Non-RCT 7 | E Abraham(2018) |  |  |  |  |  |  |  |  |  |
| Non-RCT 8 | E Abraham(2019) |  |  |  |  |  |  |  |  |  |

* **Levels of evidence**

|  |  |
| --- | --- |
|  | No (0), Serious (-1), Very serious (-2) |
| Study design | No. of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Publicationbias | Quality of evidence | Importance |
| RCT |  |  |  |  |  |  |  |  |
| Non-RCT | 9 | 0 | 0 | -1 | 0 | 0 | Low | 8 |

* **Strength of recommendation**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Balance of benefits & harms  | O |  |
| Quality of evidence |  | O |
| Values and preferences of patients | O |  |
| Resource use (Cost) | O |  |
| Acceptability of recommendation | Yes | No |
| O |  |
| Level of recommendation | Strong | Conditional |
| O |  |

**C2. What is the appropriate surgical procedure for DTC with RLN invasion?**

|  |
| --- |
| **Recommendation 12**1. Nerve-preserving procedures can be attempted if the DTC invades the RLN while vocal fold movement is retained.

(Conditional recommendation/low-quality evidence)1. The RLN may be resected if the DTC invades the RLN and vocal fold palsy is identified.

(Conditional recommendation/low-quality evidence) |

* **Final included studies**

|  |  |
| --- | --- |
| Study number | Included studies |
| Non-RCT 1 | Preservation of recurrent laryngeal nerve invaded by differentiated thyroid cancer. Ann Surg. 1997 Jul;226(1):85-91.  |
| Non-RCT 2 | Should an involved but functioning recurrent laryngeal nerve be shaved or resected in a locally advanced papillary thyroid carcinoma?Ann Surg Oncol. 2013 Sep;20(9):2951-7. |
| Non-RCT 3 | Papillary thyroid carcinoma with exclusive involvement of a functioning recurrent laryngeal nerve may be treated with shaving technique. World J Surg. 2015 Apr;39(4):969-74. |
| Non-RCT 4 | Novel surgical methods for reconstruction of the recurrent laryngeal nerve: Microscope-guided partial layer resection and intralaryngeal reconstruction of the recurrent laryngeal nerve. Surgery. 2021 May;169(5):1124-1130.  |
| Non-RCT 5 | Predictive factors and prognosis for recurrent laryngeal nerve invasion in papillary thyroid carcinoma.  Onco Targets Ther. 2017 Sep 11;10:4485-4491.  |
| Non-RCT 6 | Clinical outcomes of T4a papillary thyroid cancer with recurrent laryngeal nerve involvement: a retrospective analysis. Sci Rep. 2021 Mar 23;11(1):6707.  |
| Non-RCT 7 | Management of the recurrent laryngeal nerve in suspected and proven thyroid cancer. Otolaryngol Head Neck Surg. 1995 Jul;113(1):42-8.  |
| Non-RCT 8 | Outcome of vocal cord function after partial layer resection of the recurrent laryngeal nerve in patients with invasive papillary thyroid cancer. Surgery. 2014 Jan;155(1):184-9.  |
| Non-RCT 9 | Treatment outcomes and risk factors for recurrence after definitive surgery of locally invasive well-differentiated papillary thyroid carcinoma. 2016 Feb;26(2):262-70. |

* **Risk of bias**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstauthor (year) | Comparability of participants | Selectionof participants | Confounding | Measurementof intervention | Blinding of outcomeassessment | Measurementof outcomes | IncompleteOutcome data | Selectivereporting | Funding |
| Non-RCT 1 | Nishida, T (1997) |  |  |  |  |  |  |  |  |  |
| Non-RCT 2 | Lang, B. H (2013) |  |  |  |  |  |  |  |  |  |
| Non-RCT 3 | Lee, H. S.(2015) |  |  |  |  |  |  |  |  |  |
| Non-RCT 4 | Moritani, S(2021) |  |  |  |  |  |  |  |  |  |
| Non-RCT 5 | Chen, W(2017) |  |  |  |  |  |  |  |  |  |
| Non-RCT 6 | Na, H. S(2021) |  |  |  |  |  |  |  |  |  |
| Non-RCT 7 | Falk, S. A(1995) |  |  |  |  |  |  |  |  |  |
| Non-RCT 8 | Kihara, M(2014) |  |  |  |  |  |  |  |  |  |
| Non-RCT 9 | Kim, J. W(2016) |  |  |  |  |  |  |  |  |  |

* **Levels of evidence**

|  |  |
| --- | --- |
|  | No (0), Serious (-1), Very serious (-2) |
| Study design | No. of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Publicationbias | Quality of evidence | Importance |
| RCT |  |  |  |  |  |  |  |  |
| Non-RCT | 9 | 0 | -1 | 0 | 0 | 0 | Low | 5 |

* **Strength of recommendation**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Balance of benefits & harms  | O |  |
| Quality of evidence | Low |  |
| Values and preferences of patients | O |  |
| Resource use (Cost) | O |  |
| Acceptability of recommendation | Yes | No |
| O |  |
| Level of recommendation | Strong | Conditional |
|  | O |

**C3. What is the appropriate surgical procedure for DTC with laryngeal invasion?**

|  |
| --- |
| **Recommendation 13**1. Complete resection of invaded tissue with adequate margins should be performed for DTC with laryngeal framework invasion.

(Conditional recommendation/low-quality evidence)1. If outer cortex invasion of thyroid or cricoid cartilage is suspected, shaving resection of cartilage can be considered.

(Conditional recommendation/low-quality evidence)1. If the tumor has penetrated the thyroid or cricoid cartilage, partial or total resection of the larynx can be considered.

(Conditional recommendation/low-quality evidence) |

* **Final included studies**

|  |  |
| --- | --- |
| Study number | Included studies |
| Non-RCT 1 | Intraluminal involvement of the larynx and trachea by thyroid cancer. 1974 Oct;128(4):500-4. |
| Non-RCT 2 | Laryngotracheal invasion by thyroid-carcinoma. Ann Otol Rhinol Laryngol. 1982 Jul-Aug;91(4 Pt 1):363-9. |
| Non-RCT 3 | Resectional management of airway invasion by thyroid carcinoma. 1986 Sep;42(3):287-98.  |
| Non-RCT 4 | Surgical management of thyroid cancer invading the airway.  Ann Surg Oncol. 1997 Jul-Aug;4(5):403-8.  |
| Non-RCT 5 | Management of thyroid carcinoma invading the aerodigestive tract.  Laryngoscope. 1998 Sep;108(9):1402-7.  |
| Non-RCT 6 | Clinical outcome of different modes of resection in papillary thyroid carcinomas with laryngotracheal invasion. Arch Surg. 2006 Nov;391(6):545-9.  |
| Non-RCT 7 | Aerodigestive tract invasion by well-differentiated thyroid carcinoma: diagnosis, management, prognosis, and biology.  Laryngoscope. 2006 Jan;116(1):1-11. |
| Non-RCT 8 | Segmental laryngotracheal and tracheal resection for invasive thyroid carcinoma.  Ann Thorac Surg. 2007 Jun;83(6):1952-9. |
| Non-RCT 9 | Surgical management of laryngeal invasion by papillary thyroid carcinoma: a retrospective analysis. Thyroid. 2015 May;25(5):528-33.  |
| Non-RCT 10 | The role of laryngectomy in locally advanced thyroid carcinoma. Review of 16 cases. 2018 Apr;38(2):109-114. |
| Non-RCT 11 | Therapeutic dilemmas in the management of thyroid cancer with laryngotracheal involvement. Otolaryngol Head Neck Surg. 2000 May;122(5):763-7. |
| Non-RCT 12 | Role of surgery in treatment of advanced differentiated thyroid carcinomas. Acta Otorhinolaryngol Ital. 2007 Apr;27(2):62-7. |

* **Risk of bias**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstauthor (year) | Comparability of participants | Selectionof participants | Confounding | Measurement of intervention | Blinding of outcomeassessment | Measurementof outcomes | IncompleteOutcome data | Selectivereporting | Funding |
| Non-RCT 1 | M. Djalilian(1974) |  |  |  |  |  |  |  |  |  |
| Non-RCT 2 | V. K. Shelton(1982) |  |  |  |  |  |  |  |  |  |
| Non-RCT 3 | H. C. Grillo(1986) |  |  |  |  |  |  |  |  |  |
| Non-RCT 4 | T. M. McCarty(1997) |  |  |  |  |  |  |  |  |  |
| Non-RCT 5 | S. W. Bayles (1998) |  |  |  |  |  |  |  |  |  |
| Non-RCT 6 | N. Wada . Rino(2006) |  |  |  |  |  |  |  |  |  |
| Non-RCT 7 | J. C. McCaffrey(2006) |  |  |  |  |  |  |  |  |  |
| Non-RCT 8 | H. A. Gaissert (2007) |  |  |  |  |  |  |  |  |  |
| Non-RCT 9 | S. Moritani(2015) |  |  |  |  |  |  |  |  |  |
| Non-RCT 10 | A. I. Chala(2018) |  |  |  |  |  |  |  |  |  |
| Non-RCT 11 | K.H. Kim(2000) |  |  |  |  |  |  |  |  |  |
| Non-RCT 12 | F. Mattavelli(2007) |  |  |  |  |  |  |  |  |  |

* **Levels of evidence**

|  |  |
| --- | --- |
|  | No (0), Serious (-1), Very serious (-2) |
| Study design | No. of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Publicationbias | Quality of evidence | Importance |
| RCT |  |  |  |  |  |  |  |  |
| Non-RCT | 12 | 0 | -1 | 0 | 0 | 0 | Strong | 6 |

* **Strength of recommendation**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Balance of benefits & harms  | O |  |
| Quality of evidence | Low |  |
| Values and preferences of patients | O |  |
| Resource use (Cost) |  | O |
| Acceptability of recommendation | Yes | No |
| O |  |
| Level of recommendation | Strong | Conditional |
| O |  |

1. **Surgery for invasion of the trachea**

**D1. What is the appropriate surgical procedure for DTC with tracheal invasion?**

|  |
| --- |
| **Recommendation 14**1. If tracheal invasion of DTC is suspected, complete resection of the invaded tissue with adequate margins should be performed.

(Strong recommendation/moderate-quality evidence) |

* **Final included studies**

|  |  |
| --- | --- |
| Study number | Included studies |
| Non-RCT 1 | Clinical outcome of different modes of resection in papillary thyroid carcinomas with laryngotracheal invasion. Langenbecks Arch Surg, 2006. 391(6): p. 545-9. |
| Non-RCT 2 | Surgical management and prognosis of thyroid carcinomas invading adjacent structures. Lebanese Medical Journal, 2018. 103(5745): p. 1-7. |
| Non-RCT 3 | Pathologic staging of papillary carcinoma of the thyroid with airway invasion based on the anatomic manner of extension to the trachea: a clinicopathologic study based on 22 patients who underwent thyroidectomy and airway resection. Hum Pathol, 1993. 24(8): p. 866-70. |
| Non-RCT 4 | Surgical management of thyroid cancer invading the airway. Ann Surg Oncol, 1997. 4(5): p. 403-8 |
| Non-RCT 5 | Surgical management of tracheal invasion by differentiated thyroid cancer: how we do it. Clin Otolaryngol, 2009. 34(6): p. 565-7. |
| Non-RCT 6 | Cartilage-shaving procedure for the control of tracheal cartilage invasion by thyroid carcinoma. Head Neck, 1993. 15(4): p. 289-91. |
| Non-RCT 7 | Treatment of patients with carcinoma of the thyroid invading the airway. Arch Otolaryngol Head Neck Surg, 1994. 120(12): p. 1377-81. |
| Non-RCT 8 | Aerodigestive tract invasion by well-differentiated thyroid carcinoma: diagnosis, management, prognosis, and biology. Laryngoscope, 2006. 116(1): p. 1-11. |
| Non-RCT 9 | Local prognosis of patients with papillary thyroid carcinoma who were intra-operatively diagnosed as having minimal invasion of the trachea: a 17-year experience in a single institute. Asian J Surg, 2009. 32(2): p. 102-8. |
| Non-RCT 10 | Well-differentiated thyroid cancer with aerodigestive tract invasion: Long-term control and functional outcomes.” Head Neck, 2016. 38(1): p. 72-8. |
| Non-RCT 11 | Operative management of locally advanced, differentiated thyroid cancer.” Surgery, 2016. 160(3): p. 738-46. |
| Non-RCT 12 | Impact of extent of resection for thyroid cancer invading the aerodigestive tract on surgical morbidity, local recurrence, and cancer-specific survival. Surgery, 2010. 148(6): p. 1257-66. |
| Non-RCT 13 | Managing patients with papillary thyroid carcinoma: insights gained from the Mayo Clinic's experience of treating 2,512 consecutive patients during 1940 through 2000. Trans Am Clin Climatol Assoc, 2002. 113: p. 241-60. |

* **Risk of bias**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstauthor (year) | Comparability of participants | Selectionof participants | Confounding | Measurement of intervention | Blinding of outcomeassessment | Measurementof outcomes | IncompleteOutcome data | Selectivereporting | Funding |
| Non-RCT 1 | Wada, N.(2006) |  |  |  |  |  |  |  |  |  |
| Non-RCT 2 | Abboud, B(2018) |  |  |  |  |  |  |  |  |  |
| Non-RCT 3 | D. H. Shin(1993) |  |  |  |  |  |  |  |  |  |
| Non-RCT 4 | McCarty (1997) |  |  |  |  |  |  |  |  |  |
| Non-RCT 5 | i, Y. B.(2009) |  |  |  |  |  |  |  |  |  |
| Non-RCT 6 | Park (1993) |  |  |  |  |  |  |  |  |  |
| Non-RCT 7 | Friedman, M.(1994) |  |  |  |  |  |  |  |  |  |
| Non-RCT 8 | McCaffrey (2006) |  |  |  |  |  |  |  |  |  |
| Non-RCT 9 | Ito, Y. (2009) |  |  |  |  |  |  |  |  |  |
| Non-RCT 10 | Su, S. Y. (2016) |  |  |  |  |  |  |  |  |  |
| Non-RCT 11 | L. Y. Wang (2016) |  |  |  |  |  |  |  |  |  |
| Non-RCT 12 | M. Brauckhoff(2020) |  |  |  |  |  |  |  |  |  |
| Non-RCT 13 | I. D. Hay (2002) |  |  |  |  |  |  |  |  |  |

* **Levels of evidence**

|  |  |
| --- | --- |
|  | No (0), Serious (-1), Very serious (-2) |
| Study design | No. of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Publicationbias | Quality of evidence | Importance |
| RCT |  |  |  |  |  |  |  |  |
| Non-RCT | 13 | 0 | 0 | 0 | 0 | 0 | Moderate | 8 |

* **Strength of recommendation**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Balance of benefits & harms  | O |  |
| Quality of evidence |  | O |
| Values and preferences of patients | O |  |
| Resource use (Cost) |  | O |
| Acceptability of recommendation | Yes | No |
| O |  |
| Level of recommendation | Strong | Conditional |
|  | O |

1. Without endoluminal invasion of the trachea, shaving partial resection of the trachea can be considered.

(Conditional recommendation/low-quality evidence)

1. If endoluminal invasion of DTC is confirmed, window resection or sleeve resection should be considered.

(Conditional recommendation/low-quality evidence)

**(Conditional recommendation/low-quality evidence)**

* **Final included studies**

|  |  |
| --- | --- |
| Study number | Included studies |
| Meta-analysis 1 | Outcomes of Tracheal Resections in Well-Differentiated Thyroid Cancer-A case series and meta-analysis. World J Surg, 2021. 45(9): p. 2752-2758. |
| Meta-analysis 2 | Tracheal Resection in the Management of Thyroid Cancer: An Evidence-Based Approach. Laryngoscope, 2021. 131(4): p. 932-946 |
| Non-RCT 1 | Invasive differentiated thyroid carcinoma: tracheal resection and reconstruction procedures in the hands of the endocrine surgeon. Surgery, 1999. 126(6): p. 1078-87; discussion 1087-8. |
| Non-RCT 2 | Differentiated thyroid carcinoma with airway invasion: indication for tracheal resection based on the extent of cancer invasion. J Thorac Cardiovasc Surg, 1997. 114(1): p. 84-92. |
| Non-RCT 3 | Surgery for patients with thyroid carcinoma invading the trachea: circumferential sleeve resection followed by end-to-end anastomosis. Surgery, 1995. 117(3): p. 268-71. |
| Non-RCT 4 | Anastomosis in the absence of a suprahyoid release following circumferential sleeve resection is feasible in differentiated thyroid carcinoma patients with tracheal invasion. Oncol Lett, 2017. 14(3): p. 2822-2830. |
| Non-RCT 5 | Aggressive resection of the airway invaded by thyroid carcinoma. Br J Surg, 2005. 92(11): p. 1382-7. |
| Non-RCT 6 | Prognostic factors of locally invasive well-differentiated thyroid carcinoma involving the trachea. European Archives of Oto-Rhino-Laryngology, 2016. 273(7): p. 1919-1926. |
| Non-RCT 7 | Window Resection for Intraluminal Cricotracheal Invasion by Papillary Thyroid Carcinoma.” World J Surg, 2017. 41(7): p. 1812-1819. |
| Non-RCT 8 | Window resection of the trachea and secondary reconstruction for invasion by differentiated thyroid carcinoma. Auris Nasus Larynx, 2011. 38(2): p. 271-5. |

* **Risk of bias**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstAuthor (year) | Was an a priori design provided? | Was there dupicate study selection and data extraction? | Was a comprehensive literature search performed? | Was the status of publicatoin usea as an inclusion criterion? | List of included and exclude study | Were the characteristics of the included studies provided? | Was the scientific quality of the include studies assessed and documented? | Were the methods used to combine the findings of studies appropriate? | Publication bias assessed and discussed | Potential sources of conflict of interest |
| Meta-analysis 1 | Warshavsky(2021) | No | Yes | Yes | No | Yes | No | No | No | No | No |
| Meta-analysis 2 | M. Allen(2020) | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstauthor (year) | Comparability of participants | Selectionof participants | Confounding | Measurement of intervention | Blinding of outcomeassessment | Measurementof outcomes | IncompleteOutcome data | Selectivereporting | Funding |
| Non-RCT 1 | Nishida, T (1997) |  |  |  |  |  |  |  |  |  |
| Non-RCT 2 | Musholt(1999) |  |  |  |  |  |  |  |  |  |
| Non-RCT 3 | O. Ozak(1995) |  |  |  |  |  |  |  |  |  |
| Non-RCT 4 | Chen (2017) |  |  |  |  |  |  |  |  |  |
| Non-RCT 5 | Tsai, Y. F. (2005) |  |  |  |  |  |  |  |  |  |
| Non-RCT 6 | Kim, H.(2016) |  |  |  |  |  |  |  |  |  |
| Non-RCT 7 | Moritani(2017) |  |  |  |  |  |  |  |  |  |
| Non-RCT 8 | Ebihara, M.(2011)+ |  |  |  |  |  |  |  |  |  |

* **Levels of evidence**

|  |  |
| --- | --- |
|  | No (0), Serious (-1), Very serious (-2) |
| Study design | No. of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Publicationbias | Quality of evidence | Importance |
| RCT | 2 |  |  |  |  |  |  |  |
| Non-RCT | 8 | -1 | 0 | 0 | 0 | 0 | Conditional | 8 |

* **Strength of recommendation**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Balance of benefits & harms  | O |  |
| Quality of evidence |  | O |
| Values and preferences of patients | O |  |
| Resource use (Cost) |  | O |
| Acceptability of recommendation | Yes | No |
| O |  |
| Level of recommendation | Strong | Conditional |
|  | O |

1. **Surgery for esophageal invasion**

**E1. What is the appropriate surgical procedure for DTC with esophageal invasion?**

|  |
| --- |
| **Recommendation 15**In cases in which esophageal invasion of DTC is suspected, complete resection of the invaded tissue with adequate margins should be performed during surgery.(Conditional recommendation/low-quality evidence) |

* **Final included studies**

|  |  |
| --- | --- |
| Study number | Included studies |
| Non-RCT 1 | Aggressive surgical approach for locally invasive papillary carcinoma of the thyroid in patients over forty-five years of age. Surgery. 1986 Dec;100(6):1098-107.  |
| Non-RCT 2 | Thyroid carcinoma with tracheal or esophageal involvement: limited or maximal surgery? Surgery. 1993 Feb;113(2):166-72. |
| Non-RCT 3 | Resections of the upper aerodigestive tract for locally invasive thyroid cancer. Am J Surg. 1994 Dec;168(6):636-9. |
| Non-RCT 4 | Management of thyroid carcinoma invading the aerodigestive tract. Laryngoscope. 1998 Sep;108(9):1402-7.  |
| Non-RCT 5 | Analyses of the outcome of locally invasive papillary thyroid carcinomas. Thyroid. 1999 Oct;9(10):1017-22. |
| Non-RCT 6 | Treatment of locally aggressive well-differentiated thyroid cancer. Int Surg. 2001 Oct-Dec;86(4):213-9. |
| Non-RCT 7 | Invasive well-differentiated thyroid carcinoma: effect of treatment modalities on outcome. Otolaryngol Head Neck Surg. 2006 May;134(5):819-22.  |
| Non-RCT 8 | Role of surgery in treatment of advanced differentiated thyroid carcinomas. Acta Otorhinolaryngol Ital. 2007 Apr;27(2):62-7. |
| Non-RCT 9 | Resection margins and prognosis in locally invasive thyroid cancer. Head Neck. 2014 Jul;36(7):1034-8.  |

* **Risk of bias**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstauthor (year) | Comparability of participants | Selectionof participants | Confounding | Measurement of intervention | Blinding of outcomeassessment | MeasurementOf outcomes | Incompleteoutcomedata | Selectivereporting | Funding |
| Non-RCT 1 | K. Segal(2006) |  |  |  |  |  |  |  |  |  |
| Non-RCT 2 | F. Mattavelli (2007) |  |  |  |  |  |  |  |  |  |
| Non-RCT 3 | D. M. Hartl (2014) |  |  |  |  |  |  |  |  |  |
| Non-RCT 4 | Y. O. Fujimoto (1986) |  |  |  |  |  |  |  |  |  |
| Non-RCT 5 | D. J. B. Y. Mellière (1993) |  |  |  |  |  |  |  |  |  |
| Non-RCT 6 | A. J. Ballantyne (1994) |  |  |  |  |  |  |  |  |  |
| Non-RCT 7 | S. W. K. Bayles (1998) |  |  |  |  |  |  |  |  |  |
| Non-RCT 8 | K. S. Tanaka (1999) |  |  |  |  |  |  |  |  |  |
| Non-RCT 9 | A. S. M. Martins (2002) |  |  |  |  |  |  |  |  |  |

* **Levels of evidence**

|  |  |
| --- | --- |
|  | No (0), Serious (-1), Very serious (-2) |
| Study design | No. of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Publicationbias | Quality of evidence | Importance |
| RCT | 0 |  |  |  |  |  |  |  |
| Non-RCT | 9 | 0 | 0 | 0 | 0 | 0 | Low | 6 |

* **Strength of recommendation**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Balance of benefits & harms  | O |  |
| Quality of evidence |  | O |
| Values and preferences of patients | O |  |
| Resource use (Cost) |  | O |
| Acceptability of recommendation | Yes | No |
| O |  |
| Level of recommendation | Strong | Conditional |
|  | O |

1. **Surgery for central and lateral cervical lymph node involvement**

**F1. Is prophylactic neck dissection necessary for clinically N0 locally invasive DTC?**

|  |
| --- |
| **Recommendation 16**Prophylactic central compartment neck dissection should be considered in patients with clinically node-negative locally invasive DTC.(Conditional recommendation/moderate-quality evidence) |

* **Final included studies**

|  |  |
| --- | --- |
| Study number | Included studies |
| RCT 1 | A Randomized Controlled Clinical Trial: No Clear Benefit to Prophylactic Central Neck Dissection in Patients With Clinically Node Negative Papillary Thyroid Cancer." Ann Surg 272(3): 496-503.  |
| Meta-analysis 1 | Prophylactic central neck dissection and local recurrence in papillary thyroid cancer: A meta-analysis." Annals of Surgical Oncology 17(12): 3287-3293. |
| Meta-analysis 2 | 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): 1-133. |
| Meta-analysis 3 | The American association of endocrine surgeons guidelines for the definitive surgical management of thyroid disease in adults." Annals of Surgery 271(3): E21-E93. |
| Meta-analysis 4 | Evaluating the effectiveness of prophylactic central neck dissection with total thyroidectomy for cN0 papillary thyroid carcinoma: An updated meta-analysis." European Journal of Surgical Oncology 43(11): 1989-2000 |
| Non-RCT 1 | Prophylactic central neck dissection for papillary thyroid cancer." Br J Surg 100(3): 410-418. |
| Non-RCT 2 | Role of prophylactic central neck dissection in clinically node-negative differentiated thyroid cancer: assessment of the risk of regional recurrence." Updates Surg 69(2): 241-248 |
| Non-RCT 3 | Clinical Analysis of Cervical Lymph Node Metastasis Risk Factors and the Feasibility of Prophylactic Central Lymph Node Dissection in Papillary Thyroid Carcinoma." International Journal of Endocrinology 2021.  |
| Non-RCT 4 | Clinicopathological pattern of lymph node recurrence of papillary thyroid cancer. Implications for surgery." Int J Surg 12 Suppl 1: S194-197.  |
| Non-RCT 5 | Role of prophylactic central neck dissection in cN0 papillary thyroid cancer." Acta Otorhinolaryngol Ital 29(2): 61-69. |
| Non-RCT 6 | Prophylactic Central Neck Dissection in Papillary Thyroid Carcinoma: All Risks, No Reward." J Surg Res 264: 230-235. |
| Non-RCT 7 | Prophylactic lymph node dissection in papillary thyroid carcinoma: is there a place for lateral neck dissection?" World J Surg 37(7): 1584-1591. |
| Non-RCT 9 | The long term outcome of papillary thyroid carcinoma patients without primary central lymph node dissection: expected improvement of routine dissection." Surgery 146(6): 1188-1195. |
| Non-RCT 10 | Long-term outcomes of central neck dissection for cN0 papillary thyroid carcinoma." Am J Otolaryngol 38(5): 576-581. |
| Non-RCT 11 | Prophylactic level II neck dissection guided by frozen section for clinically node-negative papillary thyroid carcinoma: is it useful?" World J Surg 38(3): 667-672.  |
| Non-RCT 12 | Optimization of staging of the neck with prophylactic central and lateral neck dissection for papillary thyroid carcinoma." Ann Surg 255(4): 777-783.  |
| Non-RCT 13 | Influence of prophylactic neck dissection on rate of retreatment for papillary thyroid carcinoma." World J Surg 37(8): 1951-1958. |
| Non-RCT 14 | Long-term outcomes of patients with papillary thyroid cancer who did not undergo prophylactic central neck dissection." J Cancer Res Ther 16(5): 1077-1081.  |
| Non-RCT 15 | Tumor size is the strongest predictor of microscopic lymph node metastasis and lymph node recurrence of N0 papillary thyroid carcinoma." Endocr J 60(1): 113-117.  |
| Non-RCT 16 | Excellent Prognosis of Central Lymph Node Recurrence-Free Survival for cN0M0 Papillary Thyroid Carcinoma Patients Who Underwent Routine Prophylactic Central Node Dissection." World J Surg 42(8): 2462-2468.  |
| Non-RCT 17 | Prophylactic central neck dissection in 68 patients with lateral compartment metastases from well-differentiated thyroid cancer." Clin Otolaryngol 43(1): 365-369. |
| Non-RCT 18 | Prophylactic Central Neck Dissection Might Not Be Necessary in Papillary Thyroid Carcinoma: Analysis of 11,569 Cases from a Single Institution." J Am Coll Surg 222(5): 853-864. |
| Non-RCT 19 | Predictive factors and pattern of locoregional recurrence after prophylactic central neck dissection in papillary thyroid carcinoma." Ann Surg Oncol 21(13): 4181-4187. |
| Non-RCT 20 | Impact of routine unilateral central neck dissection on preablative and postablative stimulated thyroglobulin levels after total thyroidectomy in papillary thyroid carcinoma." Ann Surg Oncol 19(1): 60-67. |
| Non-RCT 21 | Clinical response to radioactive iodine therapy for prophylactic central neck dissection is not superior to total thyroidectomy alone in cN0 patients with papillary thyroid cancer." Nucl Med Commun 38(12): 1036-1040. |
| Non-RCT 22 | Risk factor analysis for predicting cervical lymph node metastasis in papillary thyroid carcinoma: a study of 966 patients." BMC Cancer 19(1): 622. |
| Non-RCT 23 | Analysis of risk factors for lateral lymph node metastasis in papillary thyroid carcinoma: a retrospective cohort study." World Journal of Otorhinolaryngology - Head and Neck Surgery.  |
| Non-RCT 24 | Risk factors of central lymph node metastasis of papillary thyroid carcinoma." Medicine (United States) 96(43).  |
| Non-RCT 25 | Prophylactic central lymph node dissection improves disease-free survival in patients with intermediate and high risk differentiated thyroid carcinoma: A retrospective analysis on 399 patients." Cancers 12(6): 1-12.  |
| Non-RCT 26 | Ipsilateral versus bilateral central neck lymph node dissection in papillary thyroid carcinoma." Ann Surg 250(3): 403-408.  |
| Non-RCT 27 | Outcomes for patients with papillary thyroid cancer who do not undergo prophylactic central neck dissection." Br J Surg 103(3): 218-225.  |
| Non-RCT 28 | Prophylactic central lymph node dissection informs the decision of radioactive iodine ablation in papillary thyroid cancer." Am J Surg 221(5): 886-892. |
| Non-RCT 29  | Ipsilateral Central Neck Dissection Plus Frozen Section Examination Versus Prophylactic Bilateral Central Neck Dissection in cN0 Papillary Thyroid Carcinoma." Ann Surg Oncol 22(7): 2302-2308. |
| Non-RCT 30 | Identifying risk factors of lateral lymph node recurrence in clinically node-negative papillary thyroid cancer." Medicine (Baltimore) 97(51): e13435.  |
| Non-RCT 31 | Role of prophylactic central neck dissection in cN0-papillary thyroid carcinoma: results from a high-prevalence area." Minerva Chir 71(3): 159-167. |
| Non-RCT 32 | Risk Factors for Central Neck Lymph Node Metastases in Micro- Versus Macro- Clinically Node Negative Papillary Thyroid Carcinoma." World J Surg 42(3): 623-629.  |
| Non-RCT 33 | Central Lymph Node Status has Significant Prognostic Value in the Clinically Node-Negative Tall-Cell Variant of Papillary Thyroid Cancer Regardless of T-Staging and Radioactive Iodine Administration: First Evidence From a Population-Based Study." Ann Surg Oncol 25(8): 2316-2322. |
| Non-RCT 34 | Prophylactic central compartment lymph node dissection in papillary thyroid carcinoma: clinical implications derived from the first prospective randomized controlled single institution study." J Clin Endocrinol Metab 100(4): 1316-1324. |
| Non-RCT 35 | Prophylactic central lymph node dissection in cN0 patients with papillary thyroid carcinoma: A retrospective study in China." Asian J Surg 39(3): 131-136.  |
| Non-RCT 36 | Optimal extent of prophylactic central neck dissection for papillary thyroid carcinoma: Comparison of unilateral versus bilateral central neck dissection." Asian J Surg 41(4): 363-369.  |
| Non-RCT 37  | Long-term Results of Observation vs Prophylactic Selective Level VI Neck Dissection for Papillary Thyroid Carcinoma at a Cancer Center." JAMA Otolaryngol Head Neck Surg 141(7): 599-606.  |
| Non-RCT 38 | Unnecessity of Routine Dissection of Right Central Lymph Nodes in cN0 Papillary Thyroid Carcinoma Located at the Left Thyroid Lobe." Frontiers in Oncology 11. |

* **Risk of bias**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstAuthor (year) | Was an a priori design provided? | Was there dupicate study selection and data extraction? | Was a comprehensive literature search performed? | Was the status of publicatoin usea as an inclusion criterion? | List of included and exclude study | Were the characteristics of the included studies provided? | Was the scientific quality of the include studies assessed and documented? | Were the methods used to combine the findings of studies appropriate? | Publication bias assessed and discussed | Potential sources of conflict of interest |
| RCT1 | Rebecca. R. Sippel (2020) | ? | ? | ? | ? | Yes | Yes | Yes | Yes | Yes | Yes |
| Meta-analysis 2 | T. Zetoune, (2010) | Yes | Yes | Yes | ? | Yes | Yes | Yes | Yes | Yes | Yes |
| Meta-analysis 2 | Haugen BR (2016) | No | Yes | Yes | ? | No | Yes | Yes | Yes | Yes | Yes |
| Meta-analysis 2 | Patel KN (2021) | Yes | Yes | No | Yes | No | Yes | Yes | No | Yes | Yes |
| Meta-analysis 2 | Zhao W (2017) | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstauthor (year) | Comparability of participants | Selectionof participants | Confounding | Measurement of intervention | Blinding of outcomeassessment | MeasurementOf outcomes | Incompleteoutcomedata | Selectivereporting | Funding |
| Non-RCT 1 | Luca Sessa(2017) |  |  |  |  |  |  |  |  |  |
| Non-RCT 2 | Wen Liu(2017) |  |  |  |  |  |  |  |  |  |
| Non-RCT 3 | Pietro Giorgio Calo)(2017) |  |  |  |  |  |  |  |  |  |
| Non-RCT 4 | Chenxi Liu(2019) |  |  |  |  |  |  |  |  |  |
| Non-RCT 5 | Romain Ducoudray(2013) |  |  |  |  |  |  |  |  |  |
| Non-RCT 6 | S. Costa(2009) |  |  |  |  |  |  |  |  |  |
| Non-RCT 7 | Songtao Zhang (2021) |  |  |  |  |  |  |  |  |  |
| Non-RCT 8 | Yasuhiro Ito (2013) |  |  |  |  |  |  |  |  |  |
| Non-RCT 9 | M Barczynski(2013) |  |  |  |  |  |  |  |  |  |
| Non-RCT 10 | T M. Kaffenberger(2017) |  |  |  |  |  |  |  |  |  |
| Non-RCT 11 | Jonathan Dismukes BS(2021) |  |  |  |  |  |  |  |  |  |
| Non-RCT 12 | S Zuniga(2009) |  |  |  |  |  |  |  |  |  |
| Non-RCT 13 | S K Kim(2016) |  |  |  |  |  |  |  |  |  |
| Non-RCT 14 | Dana M Hartl (2013) |  |  |  |  |  |  |  |  |  |
| Non-RCT 15 | G. Scerrino (2016) |  |  |  |  |  |  |  |  |  |
| Non-RCT 16 | H. S. Yoo (2018) |  |  |  |  |  |  |  |  |  |
| Non-RCT 17 | S. Xue (2016) |  |  |  |  |  |  |  |  |  |
| Non-RCT 18 | D. Viola (2015) |  |  |  |  |  |  |  |  |  |
| Non-RCT 19 | C. Nylén (2021) |  |  |  |  |  |  |  |  |  |
| Non-RCT 20 | I. J. Nixon (2016) |  |  |  |  |  |  |  |  |  |
| Non-RCT 21 | F. Medas (2020) |  |  |  |  |  |  |  |  |  |
| Non-RCT 22 | B. H. Lang (2014) |  |  |  |  |  |  |  |  |  |
| Non-RCT 23  | D. M. Hartl (2012) |  |  |  |  |  |  |  |  |  |
| Non-RCT 24 | Ito(2018) |  |  |  |  |  |  |  |  |  |
| Non-RCT 25 | Ryu (2018) |  |  |  |  |  |  |  |  |  |
| Non-RCT 26 | Lang (2012) |  |  |  |  |  |  |  |  |  |
| Non-RCT 27 | Hartl (2013) |  |  |  |  |  |  |  |  |  |
| Non-RCT 28 | Raffaelli (2015) |  |  |  |  |  |  |  |  |  |
| Non-RCT 29 | Moo (2009) |  |  |  |  |  |  |  |  |  |
| Non-RCT 30 | Senyurek (2009) |  |  |  |  |  |  |  |  |  |
| Non-RCT 31 | Giordano (2017) |  |  |  |  |  |  |   |  |  |
| Non-RCT 32 | Huang (2020) |  |  |  |  |  |  |    |  |  |
| Non-RCT 33 | Carvalho (2015) |  |  |  |  |  |  |  |  |  |
| Non-RCT 34 | Chen Y (2021) |  |  |  |  |  |  |  |  |  |
| Non-RCT 35 | Conzo G (2014) |  |  |  |  |  |  |  |  |  |
| Non-RCT 36 | Lin B (2017) |  |  |  |  |  |  |  |  |  |
| Non-RCT 37 | Lin Q (2021) |  |  |  |  |  |  |  |  |  |
| Non-RCT 38 | Shi X (2018) |  |  |  |  |  |  |  |  |  |

* **Levels of evidence**

|  |  |
| --- | --- |
|  | No (0), Serious (-1), Very serious (-2) |
| Study design | No. of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Publicationbias | Quality of evidence | Importance |
| RCT | 5 | 0 | -1 | -1 | 0 | 0 | Moderate | 5 |
| Non-RCT | 38 | 0 | -1 | -1 | -1 | 0 | Low | 7 |

* **Strength of recommendation**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Balance of benefits & harms  | O |  |
| Quality of evidence |  | O |
| Values and preferences of patients | O |  |
| Resource use (Cost) |  | O |
| Acceptability of recommendation | Yes | No |
| O |  |
| Level of recommendation | Strong | Conditional |
|  | O |

**F2. What extent of neck dissection is appropriate for DTC patients with clinically positive neck nodes?**

|  |
| --- |
| **Recommendation 17**If preoperative clinically evident central neck node metastasis is identified, ipsilateral central compartment neck dissection (level VI) is recommended.(Strong recommendation/moderate-quality evidence) |

* **Final included studies**

|  |  |
| --- | --- |
| Study number | Included studies |
| Non-RCT 1 | Differentiated Thyroid Carcinoma: Is Prophylactic Level V Neck Dissection Necessary? A Retrospective Cohort Study. Ear Nose Throat J. 2021 Apr 29: |
| Non-RCT 2 | Musacchio MJ, Kim AW, Vijungco JD, Prinz RA. Greater local recurrence occurs with "berry picking" than neck dissection in thyroid cancer. Am Surg. 2003 Mar;69(3):191-6 |
| Non-RCT 3 | Selective modified radical neck dissection for papillary thyroid cancer-is level I, II and V dissection always necessary? World J Surg. 2006 May;30(5):833-40.  |
| Non-RCT 4 | Level IIb lymph node metastasis in neck dissection for papillary thyroid carcinoma. Arch Otolaryngol Head Neck Surg. 2007 Oct;133(10):1028-30 |
| Non-RCT 5 | Elective paratracheal neck dissection for lateral metastases from papillary carcinoma of the thyroid: is it indicated? Head Neck. 2008 Mar;30(3):306-10. |
| Non-RCT 6 | Lateral cervical lymph node metastases from papillary thyroid carcinoma: pattern of nodal metastases and optimal strategy for neck dissection. Ann Surg Oncol. 2008 Apr;15(4):1177-82. |
| Non-RCT 7 | Is level IIb lymph node dissection always necessary in N1b papillary thyroid carcinoma patients? World J Surg. 2008 May;32(5):716-21. |
| Non-RCT 8 | Yanir Y, Doweck I. Regional metastases in well-differentiated thyroid carcinoma: pattern of spread. Laryngoscope. 2008 Mar;118(3):433-6 |
| Non-RCT 9 | Is a Prophylactic Central Compartment Neck Dissection Required in Papillary Thyroid Carcinoma Patients with Clinically Involved Lateral Compartment Lymph Nodes? Ann Surg Oncol. 2021 Jan;28(1):512-518.  |
| Non-RCT 10 | Therapeutic lateral neck dissection in well-differentiated thyroid cancer: Analysis on factors predicting distribution of positive nodes and prognosis. Head Neck. 2018 Feb;40(2):242-250. |
| Non-RCT 11 | Optimal surgical extent of lateral and central neck dissection for papillary thyroid carcinoma located in one lobe with clinical lateral lymph node metastasis. World J Surg Oncol. 2012 Oct 25;10:221.  |
| Non-RCT 12 |  Role of BRAF V600E mutation as an indicator of the extent of thyroidectomy and lymph node dissection in conventional papillary thyroid carcinoma. Surgery. 2015 Dec;158(6):1500-11.  |
| Non-RCT 13 | Bae SY, Yang JH, Choi MY, Choe JH, Kim JH, Kim JS. Right paraesophageal lymph node dissection in papillary thyroid carcinoma. Ann Surg Oncol. 2012 Mar;19(3):996-1000. |
| Non-RCT 14 | Patterns of cervical lymph node metastases in primary and recurrent papillary thyroid cancer. J Oncol. 2011;2011:735678. |
| Non-RCT 15 | umor above the spinal accessory nerve in papillary thyroid cancer that involves lateral neck nodes: a common occurrence. Arch Otolaryngol Head Neck Surg. 2002 Nov;128(11):1275-8.  |

* **Risk of bias**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstauthor (year) | Comparability of participants | Selectionof participants | Confounding | Measurementof intervention | Blinding of outcomeassessment | Measurementof outcomes | IncompleteOutcome data | Selectivereporting | Funding |
| Non-RCT 1 | N. N. C. Neiderman(2021) |  |  |  |  |  |  |  |  |  |
| Non-RCT 2 | M. J. Musacchio(2003) |  |  |  |  |  |  |  |  |  |
| Non-RCT 3 | N. R. Caron(2006) |  |  |  |  |  |  |  |  |  |
| Non-RCT 4 | B. J. Lee(2007 |  |  |  |  |  |  |  |  |  |
| Non-RCT 5 | A. Khafif(2008) |  |  |  |  |  |  |  |  |  |
| Non-RCT 6 | J. L. Roh(2008) |  |  |  |  |  |  |  |  |  |
| Non-RCT 7 | J. Lee(2008) |  |  |  |  |  |  |  |  |  |
| Non-RCT 8 | Y. Yanir(2008) |  |  |  |  |  |  |  |  |  |
| Non-RCT 9 | V. Harries(2020) |  |  |  |  |  |  |  |  |  |
| Non-RCT 10 | D. Lombardi(2018) |  |  |  |  |  |  |  |  |  |
| Non-RCT 11 | H. S. Keum(2012) |  |  |  |  |  |  |  |  |  |
| Non-RCT 12 | S. K. Kim(2015) |  |  |  |  |  |  |  |  |  |
| Non-RCT13 | S.Y. Bae(2012) |  |  |  |  |  |  |  |  |  |
| Non-RCT 14 | N. Ahmadi(2011) |  |  |  |  |  |  |  |  |  |
| Non-RCT 15 | J. F. Pingpank(2002) |  |  |  |  |  |  |  |  |  |

* **Levels of evidence**

|  |  |
| --- | --- |
|  | No (0), Serious (-1), Very serious (-2) |
| Study design | No. of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Publicationbias | Quality of evidence | Importance |
| RCT |  |  |  |  |  |  |  |  |
| Non-RCT | 15 | 0 | 0 | 0 | 0 | 0 | Moderate | 8 |

* **Strength of recommendation**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Balance of benefits & harms  | O |  |
| Quality of evidence |  | O |
| Values and preferences of patients | O |  |
| Resource use (Cost) |  | O |
| Acceptability of recommendation | Yes | No |
| O |  |
| Level of recommendation | Strong | Conditional |
| O |  |

|  |
| --- |
| **Recommendation 18**If lateral cervical lymph node metastasis is confirmed by biopsy, therapeutic compartment neck dissection is recommended.(Strong recommendation/moderate-quality evidence) |

* **Final included studies**

|  |  |
| --- | --- |
| Study number | Included studies |
| Non-RCT 1 | Differentiated Thyroid Carcinoma: Is Prophylactic Level V Neck Dissection Necessary? A Retrospective Cohort Study. Ear Nose Throat J. 2021 Apr 29: |
| Non-RCT 2 | Musacchio MJ, Kim AW, Vijungco JD, Prinz RA. Greater local recurrence occurs with "berry picking" than neck dissection in thyroid cancer. Am Surg. 2003 Mar;69(3):191-6 |
| Non-RCT 3 | Selective modified radical neck dissection for papillary thyroid cancer-is level I, II and V dissection always necessary? World J Surg. 2006 May;30(5):833-40.  |
| Non-RCT 4 | Level IIb lymph node metastasis in neck dissection for papillary thyroid carcinoma. Arch Otolaryngol Head Neck Surg. 2007 Oct;133(10):1028-30 |
| Non-RCT 5 | Elective paratracheal neck dissection for lateral metastases from papillary carcinoma of the thyroid: is it indicated? Head Neck. 2008 Mar;30(3):306-10. |
| Non-RCT 6 | Lateral cervical lymph node metastases from papillary thyroid carcinoma: pattern of nodal metastases and optimal strategy for neck dissection. Ann Surg Oncol. 2008 Apr;15(4):1177-82. |
| Non-RCT 7 | Is level IIb lymph node dissection always necessary in N1b papillary thyroid carcinoma patients? World J Surg. 2008 May;32(5):716-21. |
| Non-RCT 8 | Yanir Y, Doweck I. Regional metastases in well-differentiated thyroid carcinoma: pattern of spread. Laryngoscope. 2008 Mar;118(3):433-6 |
| Non-RCT 9 | Is a Prophylactic Central Compartment Neck Dissection Required in Papillary Thyroid Carcinoma Patients with Clinically Involved Lateral Compartment Lymph Nodes? Ann Surg Oncol. 2021 Jan;28(1):512-518.  |
| Non-RCT 10 | Therapeutic lateral neck dissection in well-differentiated thyroid cancer: Analysis on factors predicting distribution of positive nodes and prognosis. Head Neck. 2018 Feb;40(2):242-250. |
| Non-RCT 11 | Optimal surgical extent of lateral and central neck dissection for papillary thyroid carcinoma located in one lobe with clinical lateral lymph node metastasis. World J Surg Oncol. 2012 Oct 25;10:221.  |
| Non-RCT 12 | Patterns of cervical lymph node metastases in primary and recurrent papillary thyroid cancer. J Oncol. 2011;2011:735678. |
| Non-RCT 13 | umor above the spinal accessory nerve in papillary thyroid cancer that involves lateral neck nodes: a common occurrence. Arch Otolaryngol Head Neck Surg. 2002 Nov;128(11):1275-8.  |

* **Risk of bias**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstauthor (year) | Comparability of participants | Selectionof participants | Confounding | Measurementof intervention | Blinding of outcomeassessment | MeasurementOf outcomes | Incompleteoutcomedata | Selectivereporting | Funding |
| Non-RCT 1 | N. N. C. Neiderman(2021) |  |  |  |  |  |  |  |  |  |
| Non-RCT 2 | M. J. Musacchio(2003) |  |  |  |  |  |  |  |  |  |
| Non-RCT 3 | N. R. Caron(2006) |  |  |  |  |  |  |  |  |  |
| Non-RCT 4 | B. J. Lee(2007 |  |  |  |  |  |  |  |  | v |
| Non-RCT 5 | A. Khafif(2008) |  |  |  |  |  |  |  |  |  |
| Non-RCT 6 | J. L. Roh(2008) |  |  |  |  |  |  |  |  |  |
| Non-RCT 7 | J. Lee(2008) |  |  |  |  |  |  |  |  |  |
| Non-RCT 8 | Y. Yanir(2008) |  |  |  |  |  |  |  |  |  |
| Non-RCT 9 | V. Harries(2020) |  |  |  |  |  |  |  |  |  |
| Non-RCT 10 | D. Lombardi(2018) |  |  |  |  |  |  |  |  |  |
| Non-RCT 11 | H. S. Keum(2012) |  |  |  |  |  |  |  |  |  |
| Non-RCT 12 | N. Ahmadi(2011) |  |  |  |  |  |  |  |  |  |
| Non-RCT 13 | J. F. Pingpank(2002) |  |  |  |  |  |  |  |  |  |

* **Levels of evidence**

|  |  |
| --- | --- |
|  | No (0), Serious (-1), Very serious (-2) |
| Study design | No. of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Publicationbias | Quality of evidence | Importance |
| RCT |  |  |  |  |  |  |  |  |
| Non-RCT | 13 | 0 | 0 | 0 | 0 | 0 | Moderate | 8 |

* **Strength of recommendation**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Balance of benefits & harms  | O |  |
| Quality of evidence |  | O |
| Values and preferences of patients | O |  |
| Resource use (Cost) |  | O |
| Acceptability of recommendation | Yes | No |
| O |  |
| Level of recommendation | Strong | Conditional |
| O |  |

**F3. What is the appropriate extent of neck dissection for patients with recurrent/persistent neck node involvement in DTC?**

|  |
| --- |
| **Recommendation 19**1. If the compartment in which the lymph node has not been dissected previously has recurred, nodal clearance in a compartmental fashion should be performed.

(Conditional recommendation/low-quality evidence)1. If the compartment in which the lymph node has been dissected previously has recurred, the extent of nodal clearance should be decided after considering the oncological benefit of compartment nodal clearance and the potential risk of complications associated with revision surgery.

(Conditional recommendation/low-quality evidence) |

* **Final included studies**

|  |  |
| --- | --- |
| Study number | Included studies |
| Non-RCT 1 | Determining the extent of lateral neck dissection necessary to establish regional disease control and avoid reoperation after previous total thyroidectomy and radioactive iodine for papillary thyroid cancer Head Neck. 2012; 34(10): 1418-21. |
| Non-RCT 2 | Long-term outcome of comprehensive central compartment dissection in patients with recurrent/persistent papillary thyroid carcinoma." Thyroid. 2011; 21(12): 1309-16. |
| Non-RCT 3 | Long-Term Outcomes of Lateral Neck Dissection in Patients with Recurrent or Persistent Well-Differentiated Thyroid Cancer.” Thyroid. 2017; 27(10): 1291-1299. |
| Non-RCT 4 | Surgery for Neck Recurrence of Differentiated Thyroid Cancer: Outcomes and Risk Factors." J Clin Endocrinol Metab. 2017; 102(3): 1020-1031. |
| Non-RCT 5 | Significance of Size of Persistent/Recurrent Central Nodal Disease on Surgical Morbidity and Response to Therapy in Reoperative Neck Dissection for Papillary Thyroid Carcinoma." Thyroid. 2017; 27(1): 67-73. |

* **Risk of bias**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study No | The firstauthor (year) | Comparability of participants | Selectionof participants | Confounding | Measurement of intervention | Blinding of outcomeassessment | MeasurementOf outcomes | Incompleteoutcomedata | Selectivereporting | Funding |
| Non-RCT 1 | G.Wu (2012) |  |  |  |  |  |  |  |  |  |
| Non-RCT 2 | G.L.Clayman (2011) |  |  |  |  |  |  |  |  |  |
| Non-RCT 3 | S. B. Chinn (2017) |  |  |  |  |  |  |  |  |  |
| Non-RCT 4 | L. Lamartina (2017) |  |  |  |  |  |  |  |  |  |
| Non-RCT 5 | B. H. Lang (2017) |  |  |  |  |  |  |  |  |  |

* **Levels of evidence**

|  |  |
| --- | --- |
|  | No (0), Serious (-1), Very serious (-2) |
| Study design | No. of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Publicationbias | Quality of evidence | Importance |
| RCT |  |  |  |  |  |  |  |  |
| Non-RCT | 5 | 0 | 1 | -1 | 0 | 0 | Low | 9 |

* **Strength of recommendation**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Balance of benefits & harms  |  | O |
| Quality of evidence |  | O |
| Values and preferences of patients | O |  |
| Resource use (Cost) | O |  |
| Acceptability of recommendation | Yes | No |
| O |  |
| Level of recommendation | Strong | Conditional |
|  | O |