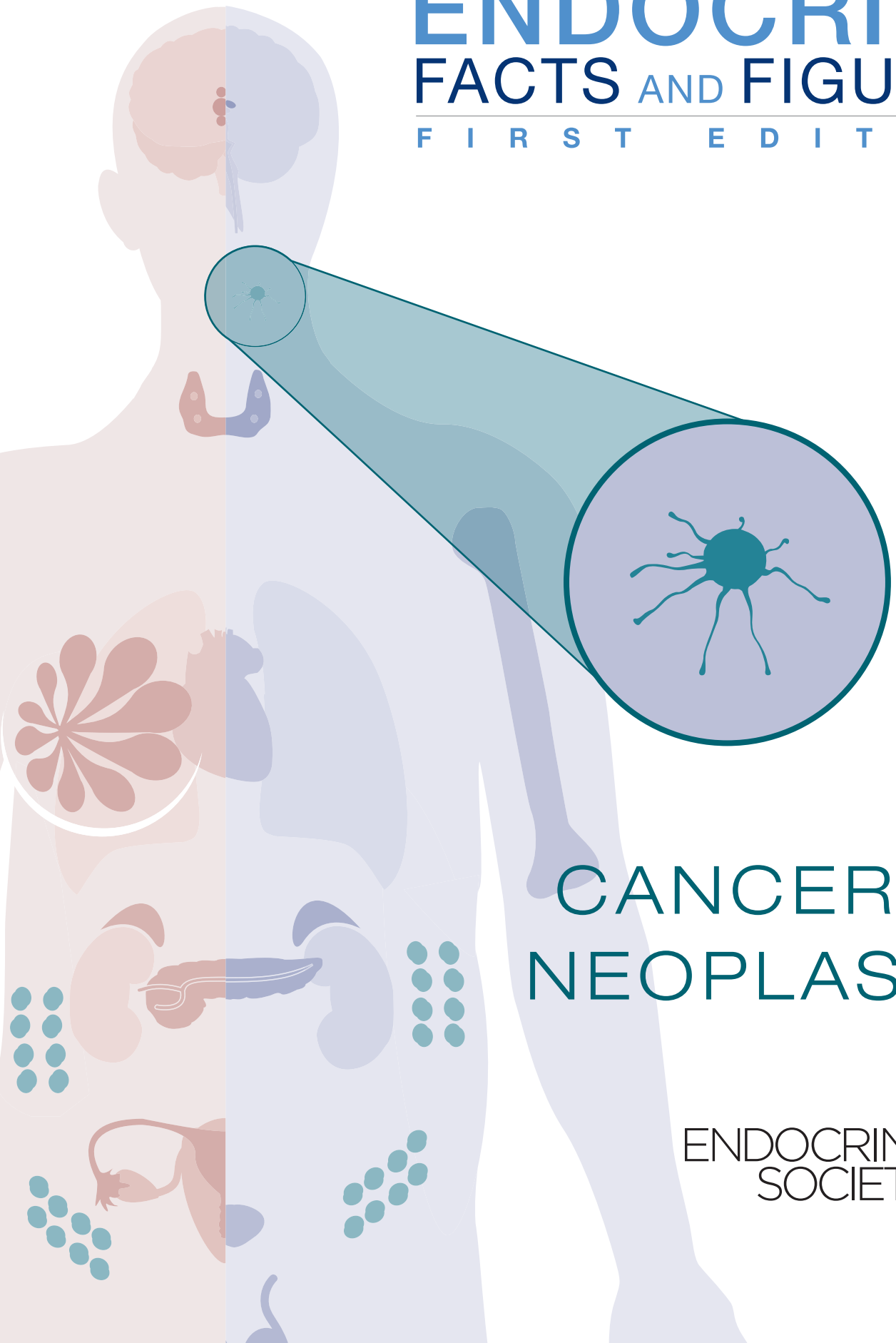
# ENDOCRINE FACTS AND FIGURES

FIRST EDITION



## CANCERS & NEOPLASIAS

ENDOCRINE SOCIETY

# THYROID CANCER

## COST BURDEN

**$1.6 BILLION**

**ESTIMATED OVERALL COST OF CARE** IN 2013 (PATIENTS DIAGNOSED AFTER 1985)[2]

**$3.1 – 3.5 BILLION**

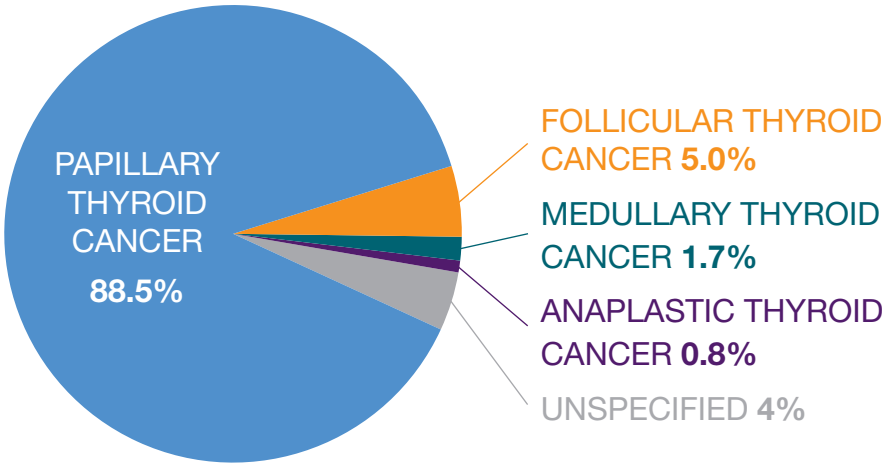
**EXPECTED COST IN 2019** (90,000 NEW CASES)[3]

## SEX DIFFERENCES


**INCIDENCE IN THE US** IN 2014[1]

## PREVALENCE

**PREVALENCE BY SUBTYPE** (2008-2012) IN THE US[1]




**726,646**

APPROXIMATE **NUMBER OF AMERICANS WITH THYROID CANCER** IN 2014[1]

## INCIDENCE

**15.04**

**US CASES** PER 100,000 IN 2014[1]


Source:

1 Howlander et al. SEER Cancer Statistics Review, 1975-2014, National Cancer Institute.

2 Lubitz et al. 2014.

3 Ascherbrook-Kilfor et al. 2013; Lubitz et al. 2014.

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## Mission Statement of the Endocrine Society

The mission of the Endocrine Society is to advance excellence in endocrinology and promote its essential and integrative role in scientific discovery, medical practice, and human health.

## About Endocrine Facts and Figures

**Endocrine Facts and Figures** is a compendium of epidemiological data and trends related to a spectrum of endocrine diseases. The data is organized into nine chapters covering the breadth of endocrinology: Adrenal, Bone and Mineral, Cancers and Neoplasias, Cardiovascular and Lipids, Diabetes, Hypothalamic-Pituitary, Obesity, Thyroid, and Reproduction and Development.

All data is sourced from peer-reviewed publications, with an additional round of review by a group of world-renowned experts in the field. Additional oversight from the Endocrine Facts and Figures Advisory Panel ensured fair and balanced coverage of data across the therapeutic areas.

The first edition of **Endocrine Facts and Figures** emphasizes data on the United States. Future updates to the report will include additional data for other countries.

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## For More Information

For more information, updates, and the online version of this report, visit: endocrinefacts.org

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## Disclaimer

This publication summarizes current scientific information about epidemiology and trends data related to a spectrum of endocrine diseases. It is not a practice guideline or systematic review. Except when specified, this publication does not represent the official policy of the Endocrine Society.



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# I OVERVIEW

This chapter presents data on Endocrine Cancers and Neoplasias, including thyroid cancer, adrenal adenomas and carcinomas, familial neoplasia syndromes, parathyroid carcinomas, pheochromocytomas and paragangliomas, and pancreatic neuroendocrine tumors. Due to the rare nature of some of these disorders, some data is not available. In addition, in instance when United States (US)-based data are limited, we present data from international studies.

# II THYROID CANCER

According to the National Cancer Institute (NCI), thyroid cancer is the most common malignant disease of the endocrine system, and in 2015 it was reported as the eighth most common cancer in the US.[1] Thyroid cancer comprises four major histological subtypes, based on whether the cancer arises in follicular (papillary, follicular, and anaplastic) or non-follicular (medullary) cell types.

## 2.1 PREVALENCE AND INCIDENCE

Based on NCI data from 2000-2012, on January 1 2012, there were 601,789 thyroid cancer cases, comprising 4.37% of all diagnosed cancers (13,776,251 cases) in the US.[2] According to the National Institute of Health's SEER 18 registries database, in 2012, the US incidence of thyroid cancer was 14.25 cases per 100,000.[3]

Importantly, the most common forms of thyroid cancer, papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) (together also referred to as differentiated thyroid cancer), have a better prognosis than the rarer anaplastic thyroid cancer (ATC).[4,5] The prevalence of thyroid cancer, by histological subtype, is shown in Table 2.1.

A 2013 study by Aschebrook-Kilfoy and colleagues using data from 1992 to 2009 SEER registries (n=59,611), reported an incidence (per 100,000) of 7.3 for PTC, 0.9 for FTC, 0.2 for MTC, and 0.1 for ATC.[6] In a follow-up study, PTC was reported to have the highest annual increase among all thyroid cancer subtypes in the US (Table 2.2).[7]

In the US, thyroid cancer (mainly PTC) is the fastest increasing cancer, with an estimated 9-fold increase since the 1930s, 3-fold since the 1970s, and almost 2-fold since the start of the millennium (Table 2.3).[2,5,8,9] Aschebrook-Kilfoy and colleagues projected that, if current trends continue, by 2019, the incidence rate per 100,000 of the US population would reach 23.[8] for PTC, 1.5 for FTC, 0.26 for MTC, and 0.12 for ATC.[6] However, it has been suggested that the rapid increase in thyroid cancer observed in the US over the last three decades may be partially due to overdiagnosis as a result of improved imaging technologies.[10,11] Furthermore, recent data suggests that rising trends in thyroid cancer may be slowing down.[12]

Periods of marked acceleration in thyroid cancer incidence are shown in Table 2.4.2.

**Table 2.1**

**Prevalence of thyroid cancer by subtypes from 1992-2012, in the US.**

| DATA SOURCE | POPULATION | HISTOLOGICAL TYPE | PREVALENCE (%) | REFERENCES |
|---|---|---|---|---|
| SEER 13 database 1992-2009 | US (n=59,611) | PTC | 84.6 | Aschebrook-Kilfoy et al. 2013[6] |
| | | FTC | 9.8 | |
| | | MTC | 2.1 | |
| | | ATC | 0.9 | |
| | | Unspecified | 2.6 | |
| SEER 18 registries 2008-2012 | US, all races, both sexes | PTC | 88.5 | Howlander et al. 2014[2] |
| | | FTC | 5.1 | |
| | | MTC | 1.7 | |
| | | ATC | 0.8 | |
| | | Unspecified | 4 | |

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; US, United States; PTC, Papillary thyroid cancer; FTC, Follicular thyroid cancer; MTC, Medullary thyroid cancer; ATC Anaplastic thyroid cancer.

**Table 2.2**

| Annual percentage change in the 4 subtypes of thyroid cancer in the US. | | | |
|---|---|---|---|
| DATA SOURCE | POPULATION | THYROID CANCER SUBTYPE | ANNUAL PERCENTAGE CHANGE (%) |
| SEER database, 1992-2009 | US (n=59,611) | PTC | +7.0 |
| | | FTC | +1.0 |
| | | MTC | +2.0 |
| | | ATC | +1.0 |
| Source: Aschebrook-Kilfoy et al. 2013[7] | | | |

Abbreviations: US, United States; SEER, Surveillance, Epidemiology, and End Results; PTC, Papillary thyroid cancer; FTC, Follicular thyroid cancer; MTC, Medullary thyroid cancer; ATC Anaplastic thyroid cancer.

**Table 2.3**

| Temporal increase in the incidence of thyroid (papillary) cancer from 1935 to 2012 in the US. | | | | | | |
|---|---|---|---|---|---|---|
| | | | INCIDENCE (PER 100,000) | | | |
| DATA SOURCE | POPULATION | THYROID CANCER TYPE | 1935-1939 | 1990-1992 | FOLD-INCREASE | REFERENCE |
| Connecticut Tumor Registry | US, incident thyroid cancer cases, both sexes (72% females, 28% males), age-adjusted (n=4,315) | Thyroid cancer | 1.6 | 8.55 | 5.3 | Zheng et al. 1996[8] |
| | | | 1973 | 2002 | | |
| SEER 9 Registries database | US, new cases of thyroid cancer, median age 46 years, 2002 (n=2,400) | Thyroid cancer | 3.6 | 8.7 | 2.4 | Davies and Welch. 2006[5] |
| | | Papillary thyroid cancer | 2.7 | 7.7 | 2.9 | |
| | | | 2000 | 2012 | | |
| SEER 18 program | US, age-adjusted to 2000 US population | Thyroid cancer | 7.4 | 14.3 | 1.9 | Howlader et al. 2014[2] |

Abbreviations: SEER, Surveillance, Epidemiology, and End Results.

Note: SEER program presents population-based data collected from 9 cancer registries in distinct areas of the United States, covers 10% of the US population in 5 states: Connecticut, Hawaii, Iowa, New Mexico, and Utah; and 4 metropolitan areas: Atlanta, Detroit, San Francisco, and Seattle.

**Table 2.4**

| Annual percentage change in invasive thyroid cancer from 1975 to 2012, in the US. | | | |
|---|---|---|---|
| DATA SOURCE | POPULATION | TIME FRAME | ANNUAL PERCENTAGE CHANGE (%) |
| SEER 9 Delay-Adjusted Incidence 1975-2012 | US, all races, both sexes | 1975-1977 | +6.3 |
| | | 1977-1980 | -6.6 |
| | | 1980-1997 | +2.4 |
| | | 1997-2009 | +6.7 |
| | | 2009-2012 | +2.3 |
| Source: National Cancer Institute. 2012[3] | | | |

Note: + denotes an increase and - denotes a decrease. Data are based on rates age-adjusted to the 2000 US standard population, from SEER 9 registries (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).

The increase in the 1970s is attributed to an increase in head and neck ionizing radiation treatment of benign childhood conditions.[8] The increase around the turn of the century is thought to be due to multiple factors, the major one being improved diagnostics (thyroid ultrasound and fine-needle aspiration technology in the 1980s) and improved detection sensitivity of subclinical small-size (≤2cm) thyroid tumors (Table 2.5).[5,13] In a retrospective cohort study of the SEER program (1988 to 2002), Davies and colleagues reported significant increases, specifically in small tumors: 49% in ≤1cm tumors and 87% in ≤2cm.[5] However, Enewold and colleagues reported increases in tumors of all sizes: 50% increase in tumors ≤1cm, 30% increase in 1.1-2cm, and a 20% increase in >2cm.[14] A combination of improved detection sensitivity and a genuine increase in incidence may explain increasing incidence of thyroid cancer.[4,14-18,19]

From 1999 to 2008, the incidence rates for thyroid tumors have increased in all SEER stages (localized, regional, distant), with the greatest increase in localized tumors (5.2 to 9.6 per 100,000). A significant increase from ~3.5 to ~5 per 100,000 was also seen in the same time frame for regional tumors.[13]

The first report of thyroid carcinomas as a common feature at autopsy, by VanderLaan in 1947, was followed by other reports of subclinical thyroid carcinomas in the general population.[20,21,22] In 1994, Ezzat and colleagues reported identifying more asymptomatic subjects with thyroid nodules by high-resolution ultrasonography (67%) and by palpation alone (21%) (Table 2.6). The concordance rate between the two techniques was 49%.[23] However, it has been suggested that Ezzat and colleagues overestimated the incidence of nodules, as 84% of the volunteers in the study were females.[24] In 2012, Ahmed and colleagues reported that in CT scans of 2,510 subjects (48.7% females), 61.5% had one or more nodules, and 38.5% had multiple nodules.[24] A 2005 study by Frates and colleagues reported that nodules were diagnosed by palpation in 4-8% of adults, by ultrasonography in 10-41% and by autopsy in 50%.[25]

Some of the most common risk factors for thyroid cancer subtypes are outlined in Table 2.7. Germline changes predisposing to thyroid cancer include *RET* mutations (Multiple Endocrine Neoplasia type 2) in MTC, *PTEN* mutations (PTEN-hamartomatous tumor syndrome, Cowden disease) in differentiated thyroid cancer, and *APC* mutations (Familial Adenomatous Polyposis) in

**Table 2.5**

**Incidence of tumor size in differentiated thyroid cancers (PTC, FTC) in the US.**

| DATA SOURCE | POPULATION | TUMOR SIZE (CM) | INCIDENCE (%) |
|---|---|---|---|
| SEER registries, 1988-2005 | US, patients with differentiated thyroid cancer (n=30,590) | <1.0 | 25 |
| | | 1-2.9 | 42 |
| | | 3-3.9 | 9 |
| | | ≥4 | 11 |
| | | unknown size | 12 |

Source: Chen et al. 2009[16]

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; US, United States; cm, centimeters.

**Table 2.6**

**Thyroid nodules identified by palpation or ultrasonography, US.**

| | | | PREVALENCE (%) | |
|---|---|---|---|---|
| DATA SOURCE | POPULATION | CONDITION | PALPATION | ULTRASONOGRAPHY |
| Asymptomatic healthy volunteers | North American, both sexes (84% female), (n=100) | no nodules | 79 | 33 |
| | | multiple nodules | 12 | 45 |
| | | solitary nodules | 9 | 22 |

Source: Ezzat et al. 1994[23]

**Table 2.7**

| Known risk factors for developing thyroid cancer by subtype. | | |
|---|---|---|
| THYROID CANCER SUBTYPE | RISK FACTORS | REFERENCE |
| PTC | Ionizing radiation exposure, history of benign nodules, goiter | Li et al. 2013[19] |
| FTC | Living in iodine-deficient region | Scopa. 2004[26] |
| MTC (sporadic) | Goiter or thyroid nodules, late menarche | Kalezic et al. 2013[27] |
| MTC (inherited) | germline mutations in RET gene | Kloos et al. 2009[28] |
| ATC | Goiter, iodine-deficiency, pre-existing well-differentiated thyroid cancer | Are et al. 2006[29]; Nagaiah et al. 2011[30]; Smallridge et al. 2012[31] |

Abbreviations: PTC, Papillary thyroid cancer; FTC, Follicular thyroid cancer; MTC, Medullary thyroid cancer; ATC Anaplastic thyroid cancer.

the cribriform-morula variant of PTC. In addition, >100 genetic alterations (mutations, insertions, deletions, rearrangements), in different molecular pathways are found in thyroid can reported cer, including somatic tumor mutations in the genes for *BRAF*, *RET* (*RET/PTC1*, *RET/PTC3*), *RAS* (*N-RAS*, *H-RAS*, *K-RAS*), *NTRK1*, *PTEN*, *PI3KCA*, *AKT1*, *TERT*, *EIF1AX*, *PPMID*, *CHEK2*, *TRK*, *CIVER1*, *MET*, *VHL*, *DICER1*, and *PRKAR1A*.[32,33-36] Some of these mutations had previously been missed by Sanger sequencing and were recently identified by Next Generation sequencing.

It has yet to be proven whether pre-operative genetic screening of tumor tissue is useful in identifying the risk of cancer recurrence or in guiding the extent of surgery, adjuvant decisions, or follow-up recommendations. The 2015 American Thyroid Association Management Guidelines acknowledge that genotyping may be useful in some situations, but do not recommend the routine use of genotyping to guide treatment.[37]

Advanced disease stage and earlier recurrence were also identified for $BRAF^{V600E}$ mutations or *RET*/PTC gene rearrangements and distant metastasis was more common in *RET*/PTC-positive cases (Table 2.8). The *RAS* and $BRAF^{K610E}$ mutations and *PAX8/PPARγ* fusions represented 25% of the cases and were associated with indolent disease and disease-free survival of 100% at 5 years.[38]

In a 2014 study examining 496 PTC cases, the most common (74.6%) pathogenic somatic mutations were in MAPK-related genes, *BRAF*, *NRAS*, *HRAS*, and *KRAS*. A *BRAF* mutation was identified in 61.7% of tumors, the most common of which was $BRAFV^{600E}$, while *RAS* was mutated in 12.9% of tumors.[33]

In a retrospective 2015 US study, the $BRAF^{V600E}$ mutation was identified in 67% of thyroid cancers (n=508); and in a 2011 study it was reported in 45% of PTC cases, 10-15% of poorly differentiated thyroid carcinomas (PDTC), and in 20-30% of ATC.[39,40] The $BRAF^{V600E}$ mutation was also reported in 63% of childhood PTC cases. A recently identified *BRAF* mutation, $BRAF^{V601E}$, comprised 5.3% of all *BRAF* mutations in thyroidectomy samples (2007-2014); 93% of these cases were PTC, and 3.4% FTC.[41]

*TERT* mutations have a higher prevalence in aggressive forms of thyroid cancer (ATC, follicular variant of PTC, and tall-cell PTC), and are absent from MTC and benign thyroid cancers (Table 2.9).[42,43] The $TERT^{C228}$ and *BRAF* mutations in combination occur at a higher prevalence than individually in PTC and ATC samples.[42] A number of publications have identified a combination of *BRAF* and *TERT* mutations in PTC tumors to be associated with a worse outcome than the single mutations, in terms of tumor aggressiveness, recurrence and mortality. These findings were recently reviewed by Liu and Xing.[43]

Around 70-75% of MTC cases arise sporadically in one lobe, and 40-50% of these sporadic cases are associated with somatic mutations in *RET*.[28] 25-30% of MTC cases are hereditary, and are linked to mutations in the *RET* oncogene (Table 2.9).[28,37,44] The subtypes of inherited MTC, associated with germline mutations, are the multiple endocrine neoplasia type 2 syndromes MEN2A (70-80%; including the subtype familial MTC or FMTC) and MEN2B (Table 2.9).[28,45] FMTC results in multifocal MTC without any pheochromocytoma or hyperparathyroidism or other clinical abnormalities, and often occurs at an older age due to the indolent nature of the cancer.[45,46]

Thyroid cancer is associated with upregulation of microRNA-146, -181, -121/222, -224 in PTC, upregulation

of microRNA-181 and -200, downregulation of miR-199 in FTC, upregulation of microRNA-17, and -221/222 and downregulation of let-7, -microRNA-30 and -29 families in ATC.[51] In an association study (US, Finland, Poland; n=608 PTC patients, n=901 controls), microRNA-146a-3p increased the risk of developing PTC (Odds Ratio OR, 1.62) in the heterozygous form (G/C) over the homozygous forms GG (OR, 0.69) or CC (OR, 0.42). Furthermore, 4.7% of tumors had undergone mutation from the homozygous to the heterozygous state.[52]

## 2.2
## COST BURDEN OF DISEASE

For thyroid cancer patients diagnosed after 1985, the estimated overall societal cost of care in 2013 was $1.6 billion (Table 2.10).[53] At the current rate of increase, there are expected to be 90,000 new cases of thyroid cancer in 2019, with an estimated cost-of-care between $3.1 billion and $3.5 billion (based on the National Cancer Institute's SEER 13 database, 1992-2009 and SEER 18 registries, 1985-2013 respectively).[6,53]

Treatment of thyroid cancer shows an increasing trend away from privately-insured Outpatient procedures towards more cost-effective Medicare-insured Outpatient procedures (Tables 2.11, 2.12).[54,55] From 1996 to 2006, the population-adjusted annual rate increased by 8.7 per 100,000 for Inpatient thyroidectomies and 45.9 per 100,000 for outpatient thyroidectomies.[54]

In a 2007 US-based study of 16,878 Health Care Utilization Project National Inpatient patients who had

**Table 2.8**

**Prevalence of genetic alterations in thyroid cancer and its subtypes, US.**

| DATA SOURCE | POPULATION | METHOD | THYROID CANCER DIAGNOSIS | FEATURES | PREVALENCE (%) |
|---|---|---|---|---|---|
| Department of Surgery, University of Pittsburgh. Thyroid cancer patients who had undergone thyroidectomy | US, mean age 49 years, both sexes (77% females), average follow-up 33 months (n=1,510) | Pre-operative ultrasound-guided needle biopsy, routine testing for genetic alterations: *BRAF*, *RAS*, *RET/PTC*, *PAX8/ PPARγ*. Total thyroidectomy for abnormal lymph node removal, if necessary. Histological metastasis or recurrent thyroid cancer tracked for 6 months after thyroidectomy | Thyroid cancer | PTC | 97 |
| | | | | Poorly differentiated thyroid cancer or ATC | 1.1 |
| | | | | *BRAF*$^{V600E}$-positive | 62 |
| | | | | *RAS*-positive | 31 |
| | | | *BRAF*$^{V600E}$ -positive PTC | Tall cell variant | 58 |
| | | | | Extrathyroidal extension | 51 |
| | | | | Lymph node metastasis | 46 |
| | | | *RAS*-positive PTC | Follicular cell variant | 87 |
| | | | | Infrequent extrathyroidal extension | 4.6 |
| | | | | Lymph node metastasis | 5.6 |
| | | | *BRAF*$^{V600E}$ or *RET*/PTC-positive thyroid cancer | Stage III/IV | 40 |
| | | | | Recurrence | 10 |
| | | | | Distant metastasis | 10.8 |
| | | | *RAS* or *PAX/PPARγ*-positive thyroid cancer | Stage III/IV | 15 |
| | | | | Recurrence | 0.7 |

Source: Yip et al. 2015[38]

Abbreviations: PTC, papillary thyroid cancer; *RET*/PTC, rearranged during transfection/papillary thyroid cancer genetic rearrangements, *PAX/PPARγ*.

**Table 2.9**

**Prevalence of mutations and genetic alterations in thyroid cancer subtypes, US and worldwide.**

| DATA SOURCE | POPULATION | THYROID CARCINOMA SUBTYPE | MUTATION | PREVALENCE (%) | REFERENCES |
|---|---|---|---|---|---|
| Review of histopathology, and genetic analysis of PTC tumors | US, children and adolescents, age 6-18 years, both sexes (74% females), (n=27) | Pediatric: PTC | fusion oncogenes: *NTRK3/ETV6*, *NTRK3*/unknown, *NTRK/TPR* | 26 | Prasad et al. 2016[47] |
| | | | RET protooncogene fusions: *RET/PTC1*, *RET/PTC3* | 22 | |
| | | | *BRAF*$^{V600E}$ | 48 | |
| Memorial Sloan-Kettering Cancer Center; 52 primary tumors; 55 recurrent and nodal and/or distant metastatic samples from patients with radioactive iodine-refractory (RAIR) differentiated thyroid cancers positive on 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET), 1983-2007 | US, DNA sequencing and mass spectrometry genotyping in patients (n=42) | Primary PDTC (n=34) | *RAS* *(NRAS; KRAS; HRAS)* | 44 (26; 9; 9) | Ricarte-Filho. 2009[32] |
| | | | *BRAF* | 9 | |
| | | | *BRAF/PIK3CA* | 3 | |
| | | | *PIK3CA* | 3 | |
| | | | *RET/PTC* | 18 | |
| | | | Unknown | 23 | |
| | | Radioactive iodine refractory FDG-PET-positive metastatic PDTC (n=23) | *BRAF* | 26 | |
| | | | *BRAF/AKT1* | 13 | |
| | | | *AKT1* | 4 | |
| | | | *RAS* *(NRAS; HRAS)* | 13 (9; 4) | |
| | | | *RET/PTC* | 9 | |
| | | | Unknown | 35 | |
| | | Primary ATC (n=18) | *BRAF* | 38 | |
| | | | *BRAF/PIK3CA* | 6 | |
| | | | *RAS* *(NRAS; HRAS)* | 23 (17; 6) | |
| | | | Unknown | 33 | |
| Published studies meta-analysis | International studies (n=2,470) | PTC | *BRAF*$^{V600E}$ | 45; higher association of mutation with PTC recurrence, lymph node metastasis, and advanced stage III/IV | Tufano et al. 2012[48]; Xing et al. 2013[49] |
| | | PTC-derived ATC | *BRAF*$^{V600E}$ | 24 | |
| Sequencing of genomic DNA isolated from thyroid tumors | US, 85 benign tumors, 257 PTC, 79 FTC, 54 ATC, 16 MTC, and 8 poorly differentiated thyroid cancer (PDTC) | PDTC | *TERT* C228T with *TERT* C250T | 43.2 | Liu et al. 2013[42]; Liu et al.2016[43] |
| | | ATC | | 40.1 | |
| | | FTC | | 17.1 | |
| | | PTC | | 11.3 | |

**Prevalence of mutations and genetic alterations in thyroid cancer subtypes, US and worldwide. (continued)**

| DATA SOURCE | POPULATION | THYROID CARCINOMA SUBTYPE | MUTATION | PREVALENCE (%) | REFERENCES |
|---|---|---|---|---|---|
| Sequencing of genomic DNA isolated from thyroid tumors | US, 85 benign tumors, 257 PTC, 79 FTC, 54 ATC, 16 MTC, 8 poorly differentiated thyroid cancer | PDTC | *TERT* C228T | 37.5 | Liu et al. 2016[43] |
| | | ATC | | 42.6 | |
| | | FTC | | 11.4 | |
| | | PTC | | 11.7 | |
| | | papillary- follicular variant | | 3.6 | |
| | | Tall cell variant | | 30.8 | |
| Sanger or next-generation sequencing | US, 266 thyroid tumors and hyperplastic nodules; 647 thyroid fine needle aspiration (FNA) samples with indeterminate cytology analyzed | ATC | *EIF1AX* mutation occurs in thyroid cancers and benign tumors; confers ~20% risk of cancer in FNA samples. | 25 | Karunamurthy et al. 2016[50] |
| | | PTC | | 2.3 | |
| | | follicular adenomas, | | 7.4 | |
| | | hyperplastic nodules, | | 1.4 | |
| | | MTC | | 0 | |
| Genomic sequencing and in informative cases also SNP arrays, exomes, RNA-seq, miRNA-seq, DNA methylation | The Cancer Genome Atlas (TCGA) project, (n=496), tumor samples and matched germline DNA from blood or normal thyroid. Informative tumors (n=390) were those analyzed on all major platforms (SNP arrays, exomes, RNA-seq, miRNA-seq, DNA methylation) | PTC | MAPK-related genes, *BRAF, NRAS*, *HRAS*, *KRAS* | 74.6 | Agrawal et al. 2014[33] |
| | | | *BRAF* | 61.7 | |
| | | | *RAS* | 12.9 | |
| | | | *MLL* | 1.7 | |
| | | | *ARID1B* | 1.0 | |
| | | | *MLL3* | 1.0 | |
| | | | PI3K and PPARγ pathway genes: PTEN, AKT1/2, PAX8/PPARG | 4.5 | |
| | | | WNT pathway related genes | 1.5 | |
| | | | Tumor suppressor genes: *TP53, RB1, NF1/2, MEN1, PTEN* | 3.7 | |
| | | | *ZFHX3* | 1.7 | |
| | | | *BDP1* | 1.2 | |
| | | | thyroglobulin | 2.7 | |
| | | | *TSHR* | 0.5 | |
| | | | *RET* fusions | 6.8 | |
| | | | *BRAF* fusions | 2.7 | |
| | | | *PAX8/PPARG* | 0.8 | |
| | | | *ETC6/NTRK3*, RBPMS/*NTRK3* fusions | 1.2 | |
| | | | THADA fusions | 1.2 | |
| | | | *ALK*-associated fusions | 0.8 | |
| | Informative tumors (n=384) subsection from all PTCs (n=496) | | *TERT* | 9.4 | |

Abbreviations: FNA, final-needle aspiration; PTC, Papillary thyroid cancer; FTC, Follicular thyroid cancer; MTC, Medullary thyroid cancer; ATC, Anaplastic thyroid cancer; PDTC, poorly differentiated thyroid cancer; FDG-PET, positive on 18F- fluorodeoxyglucose-positron emission tomography; NTRK, neurotrophic tyrosine kinase receptor.

**Table 2.10**

| Breakdown of health care costs of well-differentiated* thyroid cancer in 2013, US. | |
|---|---|
| DATA SOURCE | POPULATION |
| Diagnosis, surgery, adjuvant therapy (newly diagnosed patients) | 656,000,000 (41%) |
| Surveillance of survivors | 592,000,000 (37%) |
| Non-operative death costs attributable to thyroid cancer care | 352,000,000 (22%) |
| Source: Lubitz et al. 2014[53] | |

Note: *, Well-differentiated thyroid cancer includes papillary, follicular (including Hürthle cell) thyroid carcinomas.

**Table 2.11**

| Insurance and cost for inpatient and outpatient thyroidectomies in 1996 vs. 2006, US. | | | | |
|---|---|---|---|---|
| POPULATION | DESCRIPTION | PATIENT CATEGORY | 1996 | 2006 |
| National Survey of Ambulatory Surgery (NSAS); Nationwide Inpatient Sample (NIS) databases, 1996 and 2006 | All thyroidectomies (per year) | Outpatient | 19,099 | 30,731 |
| | | Inpatient | 52,062 | 62,200 |
| | Total thyroidectomies | All | 71,161 | 92,931 |
| | Private insurance (%) | Outpatient | 76.8 | 39.9 |
| | | Inpatient | 63.8 | 60.1 |
| | Medicare (%) | Outpatient | 17.2 | 45.7 |
| | | Inpatient | 22.8 | 25.8 |
| | Per-capita charge ($) | Outpatient | not stated | 7,222 |
| | | Inpatient | 9,934 | 22,537 |
| | Total charges ($) | Outpatient | not stated | 1.16 billion |
| | | Inpatient | 464 million | 1.37 billion |
| Source: Sun et al. 2013[54] | | | | |

Note: US Dollars were inflation adjusted from 1996 to 2006. Medicare defines outpatient as hospital stay <24 hours.

**Table 2.12**

| Change in inpatient and outpatient thyroidectomies from 1996 to 2006 in the US. | | | | | |
|---|---|---|---|---|---|
| | | | NUMBER OF PATIENTS | | CHANGE IN PATIENT NUMBER (%) |
| DATA SOURCE | POPULATION | PROCEDURE | 1996 | 2006 | 1996 TO 2006 |
| National Survey of Ambulatory Surgery and Nationwide Inpatient Sample databases, cross-sectional analysis | US, total thyroidectomy patients: n=71,161 in 1999 and 92,931 in 2006 | **All thyroidectomies** | | | |
| | | Inpatient | 52,062 | 62,200 | +20 |
| | | Outpatient [a] | 19,099 | 30,731 | +61 |
| | | **Total thyroidectomies** | | | |
| | | Inpatient | 12,314 | 27,602 | +124 |
| | | Outpatient [a] | 1840 | 2403 | +31 |
| | | **Subtotal thyroidectomies** | | | |
| | | Inpatient | 37,908 | 32,196 | -15 |
| | | Outpatient [a] | 16,194 | 26,726 | +65 |
| Source: Sun et al. 2013[54] | | | | | |

Note: [a], Medicare defines outpatient as hospital stay less than 24 hours. Percentage change is rounded up.

undergone thyroid procedures (2003-2004), the mean total cost of thyroidectomy treatment (including surgery, mean length of hospital stay) was significantly higher for Blacks ($6,587) and Hispanics ($6,294) than for Whites ($5,447).[56] Population differences are discussed further in section 2.3.

## 2.3 DEMOGRAPHIC DIFFERENCES

The prevalence of thyroid nodules detected by ultrasound in randomly selected individuals is 2-fold higher in females than males.[23,57] In 2012, Ahmed and colleagues reported that females had a higher prevalence of unsuspected single and multiple thyroid nodules (Table 2.13).[24] Patients with nodules were significantly older than those without nodules (age 64 vs. 58 years), and age correlated with the number of nodules (age 62 years for single nodule; age 66 years for multiple nodules). No association was seen between race and presence of nodules.[24]

Data from several SEER registries indicates that the overall incidence of thyroid cancer in the US is 2- to 4-fold higher in females than males (Table 2.14).

The female-to-male IRR is highest for differentiated thyroid cancer (PTC and FTC subtypes) (Table 2.15).[4]

Newly-diagnosed cases of PTC follow a normal distribution, with a peak (median 24.1% of cases) at age 50 years, whereas rates of FTC, MTC, and ATC continue to increase with age.[1,15] The highest incidence of PTC in females is at reproductive age (11.3-12.8 per 100,000, age 30-59 years), possibly due to greater detection during annual examinations, and routine thyroid testing

**Table 2.13**

**Prevalence of unsuspected thyroid nodules in an outpatient population (not diagnosed as having thyroid cancer) US.**

| | | | PREVALENCE OF NODULES (% OF PATIENTS) | |
|---|---|---|---|---|
| DATA SOURCE | POPULATION | CHARACTERISTICS | FEMALES | MALES |
| Outpatient Center, unsuspected thyroid nodules in patients not diagnosed as having thyroid disease. Detection by contrast enhanced 16- and 64-modified discrete cosine transform (MDCT) of the chest (to detect distant metastasis) | US, adults, age 18-94 years (n=2,510) | presence of nodules | 30.5 | 19.9 |
| | | multiple nodules | 13.7 | 5.8 |
| | | single nodule | 16.9 | 14.1 |

Source: Ahmed et al. 2012[24]

**Table 2.14**

**Incidence and Incidence Rate Ratio (IRR) for thyroid cancer in the US.**

| | | | INCIDENCE RATE PER 100,000 PERSON YEARS | | | |
|---|---|---|---|---|---|---|
| DATA SOURCE | POPULATION | DIAGNOSIS | FEMALES | MALES | FEMALE TO MALE INCIDENCE RATE RATIO (IRR) | REFERENCES |
| SEER 9 Registries Database 1976-2005 | US, age 0->80 years; age-adjusted rates standardized for 2000 US population, both sexes (n=44,705) | Thyroid cancer | 9.2 | 3.6 | 2.55 | Kilfoy et al. 2009[4] |
| SEER 13 Registries Database 1992-2009, | US (n=59,611) | Thyroid cancer | 12.7 | 4.5 | 2.8 | Aschebrook-Kilfoy et al. 2013[6] |
| SEER 9 Registries Database 1975-2009 | US, adults, age >18 years, ~10% of US population | Thyroid cancer | 14.9 | 3.8 | 3.9 | Davies and Welch. 2014[58] |

in prenatal care practices in some areas, whereas the highest incidence in males, at age 50-79 years (4.9-5.5 per 100,000), may reflect an increase in doctor's visits later in life.[4,59] As a result, the female-to-male incidence rate ratio (IRR) for PTC declines with age (5.0-5.4 at age 10-29 years, 3.4-3.9 at age 30-49 years, 2.44 at age 50-59 years and <2.0 above 60 years).[4] The highest incidence of FTC (SEER 9 database, 1980-2009) is in older individuals, peaking at age 70-79 years with 2.46 per 100,000 in females and 1.77 per 100,000 in males. The female-to-male IRR for FTC is highest at a younger age (4.5-5.67 at age 10-29 years, 2.9-3.76 at age 30-49, and <2.0 at age ≥50 years).[7]

The most notable increase in the incidence of thyroid cancer was in females at age 55-64 years, from 1999 to 2008 (~15 to ~33 per 100,000).[13] The American Cancer Society projected that in 2016, there would be 64,300 new cases of thyroid cancer (77% in females).[10] With a continued trend of 7% APC (1992-2009), new PTC cases in females are set to increase from 12.1 per 100,000 in 2009 to 37 per 100,000 in 2019, making thyroid cancer the third most common cancer in females in the US.[6] Analyses of race or ethnicity information from databases from 1992 to 2008, shows the lowest incidence of thyroid cancer in American Indian/Alaskan Natives (AI/AN) and Blacks, while the Female-to Male IRR are highest in Hispanics Table 2.16.

A 2016 study (newly-identified cases 2009-2011), reported highest thyroid cancer incidences in non-Hispanic Whites (22.4 vs. 8.1 per 100,000 in females vs. males; n=1,327,727) and Asians (21.5 vs. 6.8 per 100,000 in females vs. males; n=90,709). The highest incidence in the Asian group was in Filipinos (28.5 vs. 9.7 per 100,000 in females vs. males).[60] Age-adjusted rates for PTC (California Cancer Registry, 1988-2004) in Filipina and Vietnamese females were double those in Japanese females (13.7, 12.7, and 6.2 per 100,000 respectively). The place of birth was also a risk factor; Chinese and Filipina females born in the US had a higher incidence (IRR 0.48 and 0.74 respectively) than those who were foreign-born; but the opposite was seen in Japanese females (IRR 1.55).[61]

Unlike PTC, MTC and ATC, FTC shows no differences in race/ethnicity (Table 2.17). The highest Female-to-Male IRRs were: 3.55 in Hispanics, 2.53 in Asians, and ~2.0 in Whites and Blacks (Table 2.18).[15]

MTC incidence rates among Whites and Hispanics are higher than among Asians and Blacks. The female-to-male IRR was 1.47 in Asians, 1.28 in Whites, and almost equal in Hispanics (1.19) and Blacks (1.09).[15] In Whites, the Female-to-Male IRR decreased with age, most steeply for FTC, and least for MTC.[15] ATC incidence is the highest among Hispanic females and lowest among Hispanic males (female-to-male IRR 2.92).[15]

From 1999 to 2008, the incidence of thyroid cancer increased significantly in all races/ethnicities in both genders (average annual percent change, AAPC, 3.1-7.3%), except in American Indian or Alaskan Native (AI/AN) males (AAPC 0.6%).[13]

**Table 2.15**

**Incidence of subtypes in diagnosed cases of thyroid cancer from 1976 to 2005, US.**

| DATA SOURCE | POPULATION | THYROID CANCER SUBTYPES | INCIDENCE PER 100,000 PERSON YEARS | FEMALE TO MALE INCIDENCE RATE RATIO (IRR) |
|---|---|---|---|---|
| SEER 9 Registries Database 1976-2005 | US, adults, age 0->80 years, both sexes (n=44,705) | PTC | 5.1 | 2.85 |
| | | FTC | 0.8 | 2.15 |
| | | MTC | 0.2 | 1.33 |
| | | ATC | 0.1 | 1.22 |
| | | Other/unknown | 0.2 | 0.71 |

Source: Kilfoy et al. 2009[4]

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; PTC, Papillary thyroid cancer; FTC, Follicular thyroid cancer; MTC, Medullary thyroid cancer; ATC Anaplastic thyroid cancer; IRR, incidence rate ratio.

Note: SEER 9 registry includes 10% of the US population and includes following areas: Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah.

The most common SEER stages (according to American Joint Committee on Cancer, AJCC) for differentiated thyroid cancer (PTC and FTC) are localized and regional tumors (Table 2.19).[62]

A 2010 study identified significant differences in the incidence of PTC and localized, staged, thyroid cancer by race/ethnicity groups over a 13-year period (Table 2.20).

Studies of pediatric thyroid cancer (1973-2007, SEER 9 registries, n=1,360, 11% of total population) reported an incidence rate of 0.4-0.7 per 100,000 at age 0-19 years, with a higher incidence amongst girls (0.72-1.3 per 100,000) age 15-19 years (1.0-2.3 per 100,000) and Whites (0.4-0.8 per 100,000).[63] These findings in children and adolescents were confirmed in a 2014 report of cases between 2001 and 2009. While the rate of all cancers among children and adolescents (age 0-19 years)

**Table 2.16**

**Trends in thyroid cancer by race/ethnicity and gender, US.**

| DATA SOURCE | POPULATION | RACE/ETHNICITY | INCIDENCE RATE PER 100,000 PERSON YEARS | | FEMALE TO MALE INCIDENCE RATE RATIO (IRR) | REFERENCES |
|---|---|---|---|---|---|---|
| | | | FEMALES | MALES | | |
| North American Association of Central Cancer Registries (NAACCR), covering 48 States 2004-2008 | US, age 15->65 years, covering 48 States and 96% of the US population, cross-sectional rates, standardized to 2000 US population | All | 21.0 | 7.0 | 3.0 | Simard et al. 2012[13] |
| | | White | 21.6 | 7.4 | 2.9 | |
| | | Asian/Pacific Islander | 21.5 | 6.3 | 3.4 | |
| | | Hispanic (any race) | 20.4 | 5.4 | 3.8 | |
| | | Black | 12.6 | 3.8 | 3.3 | |
| | | American Indian/Alaskan Native | 10.0 | 3.1 | 3.2 | |
| SEER 13 registry database, 1992-2006 | US, age-adjusted incidence rates standardized to 2000 US population: (n=43,644*) | All | 11.3 | 4.1 | 2.8 | Aschebrook-Kilfoy et al. 2011[15] |
| | | White | 12.1 | 4.6 | 2.6 | |
| | | Asian | 12.5 | 3.9 | 3.2 | |
| | | Hispanic | 11.4 | 3.3 | 3.5 | |
| | | Black | 6.4 | 2.4 | 2.7 | |
| | | American Indian/Alaskan Native | 9.7 | 3.5 | 2.8 | |

Abbreviations: SEER, Surveillance, Epidemiology, and End Results.

Note: *, numbers are rounded up to once decimal place.

**Table 2.17**

**Incidence of papillary (PTC) and follicular (FTC) thyroid cancers by race/ethnicity, US.**

| DATA SOURCE | POPULATION | THYROID CANCER SUBTYPE | RACE/ETHNICITY | INCIDENCE (PER 100,000) |
|---|---|---|---|---|
| SEER 9 registries, 1980-2009 | US, ages 0-≥80 years; age-adjusted to the 2000 US standard population (n=45,942 PTC; n=6,410 FTC) | PTC | White | 6.41 |
| | | | Black | 3.28 |
| | | | Other* | 7.32 |
| | | FTC | White | 0.87 |
| | | | Black | 0.85 |
| | | | Other* | 0.92 |

Source: Aschebrook-Kilfoy et al. 2013[7]

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; US, United States; PTC, Papillary thyroid cancer; FTC, Follicular thyroid cancer; MTC, Medullary thyroid cancer; ATC, Anaplastic thyroid cancer.

Note: *, Other includes American Indians, Alaskan Natives, Asians, Pacific Islanders.

**Table 2.18**

**Incidence of thyroid cancer subtypes in females and males.**

| DATA SOURCE | POPULATION | THYROID CANCER SUBTYPE | RACE/ ETHNICITY | INCIDENCE RATE PER 100,000 IN FEMALES | INCIDENCE RATE PER 100,000 IN MALES | FEMALE-TO-MALE INCIDENCE RATE RATIO (IRR) |
|---|---|---|---|---|---|---|
| SEER 13 registry database, 1992-2006 | US, age-adjusted to US standard population; (n=18,523 PTC, n=2,137 FTC, n=400 MTC, n=225 ATC) | PTC | White | 10.39 | 3.58 | 2.90 |
| | | | Hispanic | 9.72 | 2.57 | 3.78 |
| | | | Asian | 10.96 | 3.20 | 3.43 |
| | | | Black | 4.9 | 1.56 | 3.14 |
| | | | AI/AN | 8.12 | 2.68 | 3.03 |
| | | FTC | White | 1.16 | 0.58 | 1.99 |
| | | | Hispanic | 1.04 | 0.29 | 3.55 |
| | | | Asian | 1.07 | 0.42 | 2.53 |
| | | | Black | 1.03 | 0.53 | 1.92 |
| | | | AI/AN | 1.02 | nc/na | nc/na |
| | | MTC | White | 0.22 | 0.17 | 1.28 |
| | | | Hispanic | 0.21 | 0.18 | 1.19 |
| | | | Asian | 0.14 | 0.10 | 1.47 |
| | | | Black | 0.11 | 0.10 | 1.09 |
| | | | AI/AN | nc/na | nc/na | nc/na |
| | | ATC | White | 0.10 | 0.10 | 0.99 |
| | | | Hispanic | 0.17 | 0.06 | 2.92 |
| | | | Asian | 0.14 | 0.11 | 1.32 |
| | | | Black | 0.13 | 0.08 | 1.65 |
| | | | AI/AN | nc/na | nc/na | nc/na |

Source: Aschebrook-Kilfoy et al. 2011[15]

Abbreviations: AI/AN American Indian/Alaskan Native; nc/na, not calculated or not applicable; SEER, Surveillance, Epidemiology, and End Results; US, United States; PTC, Papillary thyroid cancer; FTC, Follicular thyroid cancer; MTC, Medullary thyroid cancer; ATC Anaplastic thyroid cancer.

**Table 2.19**

**SEER stages of differentiated thyroid cancers, US.**

| | | | INCIDENCE PER 100,000 | |
|---|---|---|---|---|
| DATA SOURCE | POPULATION | TUMOR SEER STAGE | PTC | FTC |
| SEER 9 registry 1980-2009 | US (n=45,942 PTC, n=6,410 FTC) | Localized | 3.86 | 0.46 |
| | | Regional | 2.00 | 0.33 |
| | | Distant | 0.22 | 0.06 |
| | | Other/Unknown | 0.12 | 0.03 |

Source: Aschebrook-Kilfoy et al. 2013[7]

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; US, United States.

remained relatively stable (+0.3%), thyroid carcinomas increased at 4.9% annual percentage change (APC), with increases specifically among adolescents age 15-19 years (APC +5.7%).[64] Rates for age 0-19 years increased in all US geographic regions except the Midwest (APC: Northeast +5.8%, South +4.3%, West +6.6%). The forces driving the thyroid cancer rate increase in children and adolescents (of all race/ethnicities) (Table 2.21) have not been confirmed, but possibilities include radiation from dental radiographs, CT scans, reproductive or hormonal factors, obesity, and enhanced detection.[64]

**Table 2.20**

**Annual percent change in local staged papillary thyroid cancer (PTC) by race/ethnicity from 1992-1996 to 2000-2004, US.**

| DATA SOURCE | POPULATION | RACE/ETHNICITY | ANNUAL PERCENT CHANGE IN PTC (%) | INCREASE IN PROPORTION OF LOCAL STAGED PTC (%) |
|---|---|---|---|---|
| SEER 13, 1992-1996 and 2000-2004 | 13.8% of the US population PTC diagnosis | White | 5.6 | 14.3 |
| | | Black | 4.3 | 24 |
| | | White Hispanic | 2.8 | 14.4 |
| | | Asian | 1.5 | 4 |
| | | American Indian/ Alaska Native | 1.1 | N/A |

Source: Yu et al. 2010[18]

Abbreviations: N/A, not available; SEER, Surveillance, Epidemiology, and End Results; US, United States; PTC, Papillary thyroid cancer; FTC, Follicular thyroid cancer; MTC, Medullary thyroid cancer; ATC Anaplastic thyroid cancer.

**Table 2.21**

**Incidence of thyroid carcinomas in children and adolescents by sex and race/ethnicity, US.**

| DATA SOURCE | POPULATION | SEX OR RACE/ ETHNICITY | INCIDENCE RATE PER 1,000,000 | ANNUAL PERCENT CHANGE (APC) |
|---|---|---|---|---|
| CDC's NPCR and NCI's SEER programs, 47 population-based state cancer registries, covering 94.2% of the US populations 2001-2009, age-adjusted to 2000 US population | US, childhood and adolescent, age 0-19 years (n=120,137) | All | 6.83 | +4.9 |
| | | Males | 2.59 | +4.7 |
| | | Females | 11.31 | +4.9 |
| | | White | 7.81 | +4.0 |
| | | Black | 2.36 | +6.8 |
| | | Hispanic | 6.53 | +9.1 |

Source: Siegel et al. 2014[64]

Abbreviations: CDC, Centers for Disease Control and Prevention; NPCR, National Program of Cancer Registries; NCI, National Cancer Institute; SEER, Surveillance, Epidemiology, and End Results; US, United States.

**Table 2.22**

**Trends in 5-year relative survival rates by Race and year of diagnosis, US.**

| DATA SOURCE | POPULATION | RACE/ETHNICITY | DIAGNOSIS 1975-1977 | DIAGNOSIS 2005-2011 |
|---|---|---|---|---|
| SEER 9 registries, 1975-1977 and 2005-2011 | US, followed through 2012 | All races | 92 | 98 |
| | | White | 92 | 99 |
| | | Black | 90 | 97 |

Source: Siegel et al. 2016[10]

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; US, United States.

2.4

## LIFE EXPECTANCY AND MORTALITY

In January 2012 (SEER 1975-2007), there were an estimated 558,260 thyroid cancer survivors, or 4% of all cancer survivors (13.7 million) in the US, with a majority (78%) being female.[2,65] The excellent (90-99%) 5-year thyroid cancer survival rates (time from diagnosis to death from cancer), have increased significantly over time (Table 2.22).[1,2,10,65] Survival rates vary by cancer subtype, stage, and age at diagnosis. The 10-year relative survival rates (US, 1985-1995, n=53,856 thyroid carcinoma cases) are 93% PTC, 85% FTC, 76% Hürthle cell, 75% MTC, and 14% anaplastic/undifferentiated carcinomas.[66] For all thyroid tumor stages, the 5-year relative cancer survival rates decline with age: 99.5% age ≤45 years, 82.2% ≥75 years (2001-2007).[9] The 5-year survival rates (patients age >15 years; 2000-2007) are excellent for localized (99.8%) and regional staged tumors (97%), but poor for distant staged tumors (57.3%).[13]

Hollenbeak and colleagues suggest that the poor thyroid cancer survival rates in the Black population could be due to later disease presentation and genetic predisposition to the more aggressive forms ATC and FTC (Table 2.23).[67] While there were no differences in FTC rates among the racial groups, MTC showed the lowest survival rates in Hispanics. The worst prognosis was for ATC, with Whites having a worse rate than Blacks and Asian/Pacific Islanders (Table 2.21).

The mortality rates for thyroid cancer have remained relatively stable (0.4-0.5 per 100,000) since 1973.[1,5] A slight increase was identified in males from 2003 to 2012 (0.43 to 0.51 per 100,000).[10] The American Cancer Society projected that of the 595,690 deaths from all cancers in 2016, 1,980 (0.33%) would be from thyroid cancer; 910 (46%) in males and 1,070 (54%) in females.[10] Based on 2008-2012 US data, the number of deaths in females is higher in Asian/Pacific Islanders, Hispanics, and Blacks (0.8, 0.7, 0.6 per 100,000 respectively) than the average (0.5 per 100,000). In males, deaths in Blacks are lower at 0.4 per 100,000 than other races/ethnicities.[1] For all races and both sexes (2008-2012), the number of deaths from thyroid cancer increased with age (28.2% at age 75-84 years).[3] Orosco and colleagues in 2015, reported that age (HR, 19.2, age >45 years) and metastatic disease (HR, 13.1) were the strongest predictors of survival in differentiated thyroid cancer (Table 2.24).[68]

Differentiated thyroid cancer (PTC and FTC) is often indolent. PTC commonly metastasizes via the lymphatic system, whereas the more aggressive FTC tends to metastasize to distant sites (usually lung and bone) via vasculature. 69 Prognosis for differentiated thyroid cancer is excellent, but poor outcome can result from insensitivity to radioactive iodine treatment and to recurrences. In a 2015 study of 3,664 patients (1985-2010) who underwent surgery and adjuvant treatment, the 10-year survival rate was 96%. Mortality increased with age, with a 37-fold increase in HR from the age <45 years to age >70 years.[70] Poorly differentiated thyroid cancer, ATC, and radioactive iodine-refractory differentiated thyroid cancer have a high mortality.[32]

The *BRAF*$^{V600E}$ mutation is associated with higher recurrence rate (risk ratio 1.93), the risk ratios are 1.32 for lymph node metastasis, 1.71 for extra-thyroidal extension, and 1.7 for advanced stage III/IV.48 Relative to PTC in adults, childhood cancer has higher lymph node involvement, 10-fold higher incidence of distant metastasis, and often require extensive and repeated treatment, despite an excellent 30-year survival (90-99%).[71]

MTC is slow growing, but metastasizes locally and regionally to lymph nodes and distally to lungs, liver, and bone. For MTC, 10-year survival rates are 95% without metastasis, 40% with distant metastasis, and can vary according to the SEER stage: 100% for I, 93% for II, 71% for III, and 21% for IV. Survival rates are worse with increasing age (HR, 5.69 for age >65 years), larger tumors (HR 2.9 for >4cm), distant metastases (HR 5.7), and the number of positive regional lymph nodes (HR 3.4 for ≥16).[72] Approximately half of MTC patients have lymph node metastasis with 28% survival rate at stage IV, and 11% have distant metastasis with survival rate of 22%.[72]

ATC, a rare and extremely aggressive cancer, can metastasize to lymph nodes and distant sites early on in progression. At the time of diagnosis, the cancer is considered Stage IV (American Joint Committee on Cancer), and sub stages IVA-IVC show increasing metastasis and worsening prognosis.[30,73] ATC accounts for only 1-3% of all thyroid cancer, but 14-50% of all deaths from thyroid cancer, with median survival of 5-6 months and survival rates of 10-20% for 1-year and <5% for 5-year.[30,31]

**Table 2.23**

| Observed 5-year relative survival rates by thyroid cancer subtype, US. | | | | | | |
|---|---|---|---|---|---|---|
| DATA SOURCE | POPULATION | RACE/ETHNICITY | PTC | FTC | MTC | ATC |
| SEER 13 registry database, 1992-2004 | US (n=25,653) | White | 95.3 | 89.3 | 80.3 | 5.6 |
| | | Hispanic (white) | 94.5 | 88.4 | 73.5 | nd |
| | | Black | 91.5 | 89.7 | 85.1 | 8.9 |
| | | Asian/Pacific Islander | 94.4 | 89.9 | 88.7 | 11.4 |
| | | American Indian Natives | 96.2 | 90.5 | N/D | N/D |
| Source: Yu et al. 2010[18] | | | | | | |

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; US, United States; PTC, Papillary thyroid cancer; FTC, Follicular thyroid cancer; MTC, Medullary thyroid cancer; ATC Anaplastic thyroid cancer; N/D, not determined.

**Table 2.24**

| Mortality rate in thyroid cancer of follicular cell origin (papillary, follicular, follicular variant of papillary, anaplastic thyroid cancer, and Hürthle cell carcinoma), US. | | | |
|---|---|---|---|
| DATA SOURCE | POPULATION | RACE/ETHNICITY | PTC |
| SEER 13 registry database, 1992-2004 | US (n=25,653) | Overall mortality rate | 2.8 |
| | | Age ≥ 45 years | 94.5 |
| | | Female mortality rate | 60.8 |
| | | PTC (including follicular variant) | 38.1 |
| | | ATC | 31.3 |
| | | Other subtypes | 16.7 |
| | | FTC | 10.1 |
| | | Hürthle cell | 3.8 |
| | | Tumor size >4cm | 49.6 |
| | | Tumor size >2-4cm | 29.2 |
| | | Tumor size >1-2cm | 12.8 |
| | | Tumor size ≥1cm | 7.7 |
| | | Lymph node metastasis | 77.1 |
| | | Distant metastasis | 47 |
| Source: Nilubol et al. 2015[69] | | | |

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; US, United States; PTC, Papillary thyroid cancer; FTC, Follicular thyroid cancer; ATC Anaplastic thyroid cancer.

**Table 2.25**

| Treatment trends for papillary thyroid cancer, 1940 - 2000, US. | | | | | | |
|---|---|---|---|---|---|---|
| | | | PERCENT OF CASES BY TIME FRAME (%) | | | |
| DATA SOURCE | POPULATION | TREATMENT OR OUTCOME | 1940-1954 | 1955-1969 | 1970-1984 | 1985-2000 |
| Mayo Clinic, Minnesota | US (n=2,512) | Unilateral lobectomy | 52 | 5 | <5 | <10 |
| | | Bilateral thyroidectomy | 43 | 94 | 97 | 91 |
| | | Radioactive iodine ablation | 1 | 3 | 32 | 46 |
| | | 15 years cause-specific mortality | 7.4 | 4.9 | 4.0 | 2.7 |
| | | 15-year recurrence | 18.4 | 7.6 | 11.0 | 11.7 |
| Source: Hay et al. 2002[74] | | | | | | |

2.5

## KEY TRENDS AND HEALTH OUTCOMES

A study of differentiated thyroid cancer between 1940 and 2000 identified an improvement in the 15-year cause-specific mortality and 15-year recurrence rate. Importantly, while this is thought to be due to a trend away from unilateral lobectomy, towards bilateral thyroidectomy, the 2015 ATA guidelines now allow for lobectomy in properly selected patients (Table 2.25).[74]

Thyroidectomy is the main treatment for both benign and malignant thyroid cancers, although the surgeon's experience in performing thyroidectomies (i.e. patient volume) influences patient outcome (Table 2.26).[75]

Surgeon volume may also partially explain racial disparities in clinical and economic outcomes of thyroidectomies (Table 2.27). Highest-volume surgeons (>100 cases per year) performed merely 5% of the thyroidectomies, but 90% of their patients were White.[56]

For PTC (that can metastasize to cervical lymph nodes), the most common initial therapies are surgery (total thyroidectomy) with or without $^{131}$I radioactive iodine treatment. For more uncommon aggressive cases, treatment may also include external beam therapy and cytotoxic chemotherapy, traditionally including doxorubicin (as monotherpy or with cisplatin).[7,76] Due to toxic side-effects, partial response rate (25-37%), and rarely complete remission, doxorubicin and/or cisplatin are used for patients with rapidly progressive metastatic disease or if patient conditions are not suitable for surgery, radioiodine, external beam therapy, or where tyrosine kinase inhibitors cannot be used or have failed.[77] However, as the cancer metastasizes to distant sites, a drop in survival rate can be expected, as surgery and radioactive iodine are no longer effective. The 10-year survival rate in differentiated thyroid cancer after distant metastasis drops to between 25% and 42%.[78,79]

In the last two decades, somatic and germline genetic mutations have been discovered in distinct biological

**Table 2.26**

**Clinical outcomes from thyroidectomy influenced by experience of surgeon, US.**

| DATA SOURCE | POPULATION | SURGEON EXPERIENCE (THYROIDECTOMY CASES/YEAR) | MEAN LENGTH OF HOSPITAL STAY (DAYS) | COMPLICATION RATE |
|---|---|---|---|---|
| Non-federal acute care hospitals in Maryland, benign or malignant thyroidectomies, cross-sectional analysis of hospital discharge data 1991-1996 | US, Maryland, age >18 years (n=5,860) | 1-9 | 1.9 | 8.6 |
| | | 10-29 | 1.7 | 6.1 |
| | | 30-100 | 1.7 | 6.1 |
| | | >100 | 1.4 | 5.1 |

Source: Sosa et al. 1998[75]

**Table 2.27**

**Racial disparities in clinical outcomes from thyroidectomy, US.**

| DATA SOURCE | POPULATION | RACE/ ETHNICITY | PATIENTS (%) | MEAN LENGTH OF HOSPITAL STAY (DAYS) | IN-HOSPITAL MORTALITY | COMPLICATION RATE | SURGERY BY LOWEST VOLUME SURGEONS (1-9 CASES/ YEAR) |
|---|---|---|---|---|---|---|---|
| Health Care Utilization Project National Inpatient samples, selected samples undergone thyroid procedures, 2003-2004 | US (n=16,878) | White | 71 | 1.8 | 0.1 | 3.8 | 44 |
| | | Black | 14 | 0.5* | 0.4* | 4.9 | 52 |
| | | Hispanic | 9 | 2.2 | 0.1 | 3.6 | 55 |

Source: Sosa et al. 2007[56]

Note: *, denotes statistically significant data relative to the white population.

pathways associated with development and progression of thyroid cancer. Therapies targeting some of these pathways have already proved to be effective in clinical trials, including for the tyroisine kinase inhibitors axitinib, lenvatinib, motesanib, pazopanib, sorafenib, sunitinib, and vandetinib. In addition to the approval of sorafenib and lenvatinib by the FDA, the National Comprehensive Cancer Network (NCCN) Guidelines allow for the use of other tyroisine kinase inhibitors for thyroid cancer (see below).[80]

Mutations in *BRAF* are found in ~45% of sporadic PTCs with the *BRAF*$^{V600E}$ mutation making up >90% of these cases.[81] In a 2015 retrospective study (2,099 patients, 16 international medical centers), the mutation *BRAF*$^{V600E}$ (prevalence 48%) was associated with increased risk of PTC recurrence (recurrence rates 47.7 for mutation-positive versus 26.0 for mutation-negative per 100,000), with HR of 1.[82.82,83]

*Raf* kinase inhibitors, can inhibit growth of poorly differentiated thyroid cancer cell lines with *RET* or *Raf* mutations, and include the multikinase inhibitor sorafenib (targeting *VEGFR-1*, *VEGFR-2*, *VEGFR-3*, *RET*, and *FLT3*, *c-KIT*, wildtype and mutant *BRAF*). Sorafenib, approved by the FDA in 2013, improved progression-free survival in clinical trials for locally recurrent, or metastatic, radioiodine-refractory PTC (*BRAF*$^{V600E}$) progressive differentiated thyroid cancer (Table 2.28).[76,81,84]

MTCs are more invasive and metastatic than PTC and FTC; at diagnosis, 50% of patients have neck lymph node metastases and 20% have distant metastases.[85] Radioactive-iodine cannot effectively treat metastases in MTC as the cancer originates in non-follicular C cells, which do not absorb iodine; therefore, repeated surgery (total thyroidectomy) is performed on recurrent tumors.[86] Moreover, 25% of MTCs are positive for inheritable *RET* mutations.[28,85] *RET* encodes a tyrosine kinase receptor, and therefore, tyrosine kinase inhibitors are being explored to manage advanced metastases; vandetanib and carbozantinib are already FDA-approved. Some of the current thyroid cancer treatments and their outcomes are summarized in Table 2.28. Vandetanib is a multi-kinase selective inhibitor that targets *VEGFR-2*, *VEGFR-3*, *EGFR*, and *RET* kinases, and was FDA approved in 2011 for the treatment of MTC in unresectable, locally advanced, or metastatic MTC (Table 2.28).[76,81] Lenvatinib is a multi-kinase inhibitor of *VEGFR 1,2,3 FGFR 1-4*, *PDGFRa*, *RET*, *KIT*; approved by the FDA in February 2015 to treat locally recurrent or metastatic or progressive RAI-refractory differentiated thyroid cancer (PTC, PDTC, FTC, Hürthle cell) (Table 2.27).[76,87-89] Cabozantinib (XL184) is a tyrosine kinase inhibitor, that targets multiple pathways, via *VEGFR-2*, *RET*, and mesenchymal-epithelial transition factor *c-MET*.[90,91] It was approved by the FDA in November 2012 for the treatment of progressive metastatic MTC (Table 2.28).[76]

Gene rearrangements involving the *PPAR* nuclear receptor, such as the *PAX8/PPARγ* translocation, have been reported in ~35% of FTC, and *PPAR-γ* agonist may be effective treatment in these cases (Table 2.28).[92]

# III ADRENAL ADENOMAS AND CARCINOMAS

The three major types of adrenal tumors are adrenal adenomas, adrenal hyperplasias, and adrenocortical carcinomas. Adrenal adenomas included in this section are non-functioning (non-hormone secreting), cortisol-producing (Cushing's syndrome), and aldosterone-producing (including Conn's adenoma) adenomas. Adrenal hyperplasias, technically referring to increased ACTH-independent cell growth of parts of the adrenal cortex, included are cortisol-producing (macronodular and micronodular) and aldosterone-producing (familial hyperaldosteronism types I, II and III). Both unilateral aldosterone-producing adenomas and bilateral adrenal hyperplasias can give rise to primary aldosteronism. Adrenocortocol carcinomas can arise in patients with hereditay predisposition such as Lynch syndrome, Li-Fraumeni syndrome, Multiple Endocrine Neoplasia type 1, Beckwith-Wiedemann syndrome and Familial Adenomatous Polyposis.

## 3.1 PREVALENCE AND INCIDENCE

Estimates of the prevalence of adrenal tumors vary greatly according to the screening method and the population examined. Most adrenal tumors are incidentally discovered by imaging procedures, conducted for different purposes, and are therefore termed incidentalomas. Adrenal incidentalomas can cover a range of phenotypes from non-functioning adenomas or functioning (hormone-secreting), associated with primary aldosteronism or autonomous cortisol production to carcinomas.[100-102] The prevalence of adrenal incidentalomas by subtypes is shown in Table 3.1.

**Table 2.28**

| Treatments and outcomes by thyroid cancer subtypes after surgery, radiotherapy, chemotherapy, and/or targeted therapies, US and worldwide. | | | | | |
|---|---|---|---|---|---|
| DATA SOURCE | POPULATION | CHARACTERISTICS | TREATMENT | OUTCOME | REFERENCES |
| DIFFERENTIATED THYROID CANCER (DTC) (PAPILLARY AND FOLLICULAR) | | | | | |
| Prospective multi-institutional registry, 1987-2012 | US, n=4,941 differentiated thyroid cancer; 3,268 thyroid hormone suppression therapy; 6-year median follow-up | 88% PTC, 8% FTC, 4% Hürthle cell cancer | Total or near-total thyroidectomy, radioactive iodine, thyroid hormone suppression therapy | Overall survival improved in stage III by radioactive iodine (risk ratio 0.66), and in stage IV by total/near-total thyroidectomy (0.66) followed by radioactive iodine (risk ratio 0.7). Only total/near-total thyroidectomy improved both overall survival (risk ratio 0.13, 0.09,0.13, 0.33 in stages I-IV) and disease-free survival (risk ratio 0.52, 0.4, 0.18 in stages I-III). Radioactive iodine was not beneficial in low-risk patients. | Carhill et al. 2015[93] |
| Phase III trial, randomized, double-blind, multicenter study, Aug 2011-Oct 2012 | Worldwide; Lenvtinib n=261, placebo n=13; 124mg/day oral dose, in 28 cycles | DTC refractory to $^{131}$I iodine: PTC, PDTC, FTC, Hürthle cell | Targeted therapy: Lenvatinib, | Progression-free survival 15 months (median). Partial response 15% (median duration 7.5 months), stable disease (> 6 months) 56%. | Schlumberger et al. 2015[87] |
| Phase II clinical trial, 2004-2007 | US, n=41 PTC, *BRAF* mutation in 77% of 22 PTCs analyzed. | Metastatic PTC | Targeted therapy: Sorafenib | Progression-free survival 15 months (median). Partial response 15% (median duration 7.5 months), stable disease (> 6 months) 56%. | Kloos et al. 2009[94] |
| Systemic literature review (Dec 2012) in 7 phase II or open label trials | Worldwide, n=219 (in total 7 trials), n=159 DTC, n=52 MTC, n=8 ATC | First-line treatment for radioiodine-resistant metastatic differentiated thyroid cancer (DTC) | Targeted therapy: Sorafenib | Progression-free survival disease stabilization but no complete remission. Overall: 21% partial response (21% DTC, 22% MTC, 13% ATC), 60% stable disease, 20% progressive disease (93% MTC and 79% DTC for overall clinical benefit i.e. partial response and stable disease response). Drug discontinued in 16%, and dose reduction in 56%. Mortality not related to progressive disease in 4%. | Thomas et al. 2014[95] |
| PAPILLARY THYROID CANCER | | | | | |
| Thyroid carcinomas of follicular cell origin who had undergone thyroidectomy for PTC and received follow-up care, 1974-2009 | Washington University, School of Medicine, age 5.8-84.6 years (n=508) | Average tumor size 2cm, 54.8% disease limited to thyroid, 42.2% disease in neck nodes and thyroid, 2.8% distant metastases to lung, 0.2% disease in thyroid and bone metastasis. Mean follow-up 9.8 years. *BRAF*$^{V600E}$ mutation (n=508) in ~70% | Surgery: Total thyroidectomy 97%, lobectomy or partial resection 3%, thyroid biopsy only 0.6%. Surgery for metastatic lymph nodes 57%, neck lymph node removal 43%. Postoperative $^{131}$I 94%. | Overall survival rate: 95.4% for 10 years, 84.5%. Disease-specific survival: 97.4% at 10 years, 96.8% 20 years. Recurrence-free survival 88.8% at 10 years, 80.3% 20 years. Mortality: 10%, mortality from thyroid cancer 2.6%. No association of mutation with recurrence-free survival or disease-specific survival | Henke et al. 2015[39] |

| Treatments and outcomes by thyroid cancer subtypes after surgery, radiotherapy, chemotherapy, and/or targeted therapies, US and worldwide. (continued) | | | | | |
|---|---|---|---|---|---|
| DATA SOURCE | POPULATION | CHARACTERISTICS | TREATMENT | OUTCOME | REFERENCES |
| MEDULLARY THYROID CANCER | | | | | |
| National Cancer database, 1985-2005 | US, both sexes (n=2,968) | 38.4% regional lymph node positive and 65.8% resected, 11.1% distant metastases | Surgery: 83.0% total thyroidectomy, 10.2% lobectomy, 6.8% no surgery | No effect of surgery on survival in tumors <2cm/no distant metastases. Tumors >2cm/no distant metastases. Mortality: 61.1% no surgery, 30.4% lobectomy, 21.8% total thyroidectomy. For any tumor size + distant metastases: lower mortality (70.1%) with total thyroidectomy + regional lymph nodes resected than total thyroidectomy (89.7), or no surgery (85.1) | Esfandiari et al. 2014[72] |
| Phase III randomized, double-blinded trial: Dec 2006-Nov 2007, with median follow up of 24 months | Multicenter, adults, mean age 52 years, 90% sporadic, 95% metastatic (n=331: 231 vandetanib, 100 plascebo) | Presenting with unresectable locally advanced or metastatic, hereditary or sporadic medullary thyroid carcinoma (MTC). Tumor sample submission or RET germline mutation. Serum calcitonin ≥500pg/ml | Targeted therapy: vandetanib starting oral dose 300mg/day or placebo. | At 24 months follow-up: disease progressed in 37%; mortality 15%; Overall response rate 44%. Progression-free survival (PFS) vandetanib 30 months, placebo 19 months. Adverse events more common with vandetanib than placebo. Long-term use required as non-curative | Wells et al. 2012[96] |
| Phase II/II clinical trials | Children age 5-12 years and adolescents age 13-18 years (n=16) | Locally advanced or metastatic medullary thyroid carcinoma (MTC) | Targeted therapy: Vandetanib in MTC and germline *RET* mutations, oral dose 100mg/m2, daily | Partial response in 47% | Fox et al. 2013[97] |
| Phase III multicenter trial | Patients with radiological progression before enrollment (n=330) | Metastatic medullary thyroid carcinoma (MTC) | Targeted therapy: Cabozantinib 140mg/day orally. | Overall response rate for cabozantinib 28%. Patients alive and progression-free at 1 year: 47.3% cabozantinib and 7.2% placebo. Progression-free survival cabozantinib 11.2 months, placebo 4 months. Adverse events noted in most cases. Long-term use required as not curative | Elisei et al. 2013[90] |

| Treatments and outcomes by thyroid cancer subtypes after surgery, radiotherapy, chemotherapy, and/or targeted therapies, US and worldwide. (continued) | | | | | |
|---|---|---|---|---|---|
| DATA SOURCE | POPULATION | CHARACTERISTICS | TREATMENT | OUTCOME | REFERENCES |
| ANAPLASTIC THYROID CANCER | | | | | |
| National Cancer Center Database, diagnosis Jan 1998 to Dec 2012 | US, 68.4% ≥65 years, 75% White, 44.7% positive nodes, 41.6% metastatic disease, 8.9% primary tumor confined to thyroid (n=3,552) | 50.5% no surgery, 23.2% total thyroidectomy, 26.3% other surgery, 58.7% external-beam. Radiotherapy, 41.6% chemotherapy, 33.1% radiotherapy and chemotherapy. Median follow-up 46.7 months for those alive or 3.5 months. | Thyroidectomy, radiotherapy, chemotherapy | Survived 2 years: total thyroidectomy 18.6%, other surgery 11.9%, no surgery 5.0%; radiotherapy ≥59.4 Gy 21.6%, 36.1-59.3 Gy 10.9%, ≤36 Gy 3.2%, none 7.1%; chemotherapy 13.1%, no chemotherapy 7.3%. | Glaser et al. 2016[73] |
| National Cancer Database, 2003-2006 | US (n=345) | Anaplastic thyroid carcinoma (ATC) | thyroid resection | Median survival rates were 9.7, 4.2, and 3.4 months for stages IV-A, IV-B and IV-C, respectively | Goffredo et al. 2015[98] |
| Multicenter phase 1 trial | US, adults age 43-82 years (n=15) | Advanced Anaplastic thyroid carcinoma (ATC), most partial tumor resection, 53% radiotherapy, 26% chemotherapy 20% coexisting PTC. | Combinatorial therapy: *PPAR-γ* agonist efatutazone with paclitaxel | 1/15 patients showed durable RECIST response, 2/15 showed ~42% improved time to progression and survival, 8/15 showed periods of disease stabilization; adverse events included edemas: fluid retention. Promising results-further trials necessary. | Smallridge et al. 2013[99] |

Abbreviations: CEA, carcinoembryonic antigen; *c-MET*, mesenchymal-epithelial transition factor; DTC, differentiated thyroid cancer; *EGFR*, Epidermal Growth Factor Receptor; FDA, United States Food and Drug Administration; *FGFR 1-4*, Fibroblast growth factor receptor; FMTC, familial medullary thyroid carcinoma; Gy, Gray unit; HR, hazard ratio for progression or death; *KIT*, transmembrane receptor tyrosine kinase; MEN2A, MEN2B, multiple endocrine neoplasias; *PDGFR*, platelet-derived growth factor receptor; *PPAR-γ*, peroxisome proliferator-activated receptor-gamma; RECIST, Response Evaluation Criteria in Solid Tumors; *RET*, Rearranged during transfection; *VEGFR*, vascular endothelial growth factor.

**Table 3.1**

| Prevalence of adrenal tumor subtypes determined by computed tomography (CT) scans from literature reviews, worldwide. | | | |
|---|---|---|---|
| ADRENAL INCIDENTALOMA | ADRENAL INCIDENTALOMA SUBTYPES | PROPORTION OF ALL ADRENAL INCIDENTALOMAS (%) | REFERENCES |
| Adrenal adenomas | Non-functioning adenomas | 58.3-86 | Anagnostis et al. 2009[100]; Giordano et al. 2010[102] Di Dalmazi et al. 2012[103]; Vassilatou et al. 2009[104]; Akehi et. al. 2013[105]; Libe et al. 2002[106] |
| | Cortisol-producing adenomas (subclinical Cushing's syndrome) | 1-41 | |
| | Aldosterone-producing adenomas | 1.6-3.3 | Anagnostis et al. 2009[100]; Amar et al. 2010[107] |
| Adrenal hyperplasias | N/A | 7-17 | Anagnostis et al. 2009[100]; Barzon et al. 2003[101]; |
| Adrenocortical carcinomas | N/A | 1.2-11 | Anagnostis et al. 2009[100]; Barzon et al. 2003[101]; Bilimoria et al. 2008[108] |

Abbreviations: N/A, not applicable.

Detection frequency of adrenal tumors has increased in recent years with increasing use of sensitive imaging methods: computed tomography (CT) scans, magnetic resonance imaging (MRI), and ultrasonography (Table 3.2).[101] Adrenal incidentalomas are among the most prevalent tumors in humans, being detected in 0.1% of the normal population by ultrasound, and in 1-4% by abdominal imaging analysis (CT scans, MRI and ultrasound).[109,110] Worldwide studies roughly estimate the same prevalence at autopsy (1.4 to 6%) and in CT scans (0.35 to 6%).[100-102] In a systemic review, adenomas and adrenocortical carcinomas comprised 41% and up to 10% of all incidentalomas, respectively.[109] However, these numbers likely overestimate the presence of adrenocortical cancer, which is a very rare disease.[111]

An estimated 10% of subjects with adrenal incidentalomas secrete excess cortisol in the absence of clinically overt Cushing's syndrome, defined as subclinical Cushing's syndrome; and while most cases may undergo extensive screening, an adrenalectomy may be performed in some. However, the incidence of subclinical Cushing's syndrome is 79 per 100,000 persons, while clinical adrenal Cushing's syndrome is very rare (~1 person per 100,000).[112] As the majority of incidentalomas will never progress to clinical Cushing's syndrome, some authors suggest that extensive screening and adrenalectomy are unnecessary.[113]

Aldosterone-producing adenomas (Conn's adenoma or aldosternoma) are most commonly small (<2cm) tumors, arising sporadically. It is thought to comprise

**Table 3.2**

**Prevalence of adrenal adenomas and adrenocortical carcinomas.**

| DATA SOURCE | METHOD | POPULATION | PATIENTS | PREVALENCE (%) | PROPORTION OF SUBTYPES (%) | REFERENCES |
|---|---|---|---|---|---|---|
| Adrenal incidentalomas | Literature review | Worldwide, n=71,206 patients | Abdominal CT scan in patients | 0.5 – 2 | | Barzon et al. 2003[101] |
| | | | Autopsy studies | 1 - 8.7 (avg. 2.3) | | |
| High-resolution CT scan of chest in patients in a screening program for lung cancer | Prospective study | Italy, adults, age 50-79 years, median age 58 years, no adrenal hyperfunction (n=520) | Benign adrenal mass | 4.2 | | Bovio et al. 2006[116] |
| | | | Malignant adrenal mass | 0.2 | | |
| CT scans and biochemical function analysis on adrenal masses | Retrospective study | US, Adrenal incidentalomas >1cm, 1985-1989 (n=172) | Cortisol-producing tumors | 0.01 | | Herrera et al. 1991[124] |
| | | | Adrenal carcinomas | 0.029 | | |
| Incidentalomas discovered by CT scan | Retrospective study | Korea, adults, age 20-86 years, 55.2% females, 2005-2012 (n=834) | Non-functioning incidentalomas | | 82.2 | Kim et al. 2013[125] |
| | | | Subclinical Cushing's syndrome | | 6.0 | |
| | | | Aldosterone-producing adenomas | | 4.6 | |
| | | | Pheochromocytoma | | 7.2 | |
| Adrenal incidentalomas (ultrasound, CT scan or MRI) | Prospective study | Turkey, age 29-78 years, mean age 54.5 years, 71% female (n=70) | Non-functioning incidentalomas | | 94.3 | Emral et al. 2003[126] |
| | | | Subclinical Cushing's syndrome | | 5.7 | |

33-67% of primary aldosteronism, which itself accounts for up to 10% of all hypertension patients.[114] In a study of 71 adrenal glands removed from unilateral primary aldosteronism cases in Italy, 77.5% of patients had a single nodule and 22.5% had multinodular hyperplasia.[115]

Adrenocortical carcinomas are rare, aggressive malignancies (Table 3.2), with an estimated incidence of 0.5-2.0 per million (300 cases per year) in the US, and 0.7-2.0 million worldwide.[116-118] According to the SEER database (1973 and 2000), the age-adjusted incidence of adrenocortical carcinoma in the US was 0.72 per million, accounting for only a small fraction of all adrenal incidentalomas, and comprising 0.02% - 0.2% of all cancers reported annually in adults.[119-121] Childhood adrenocortical carcinomas have a worldwide incidence of 0.2-0.3 per million and represent 0.2-1.3% of all childhood cancers.[122,123]

***Temporal Increase***

A temporal increase in the prevalence of incidentalomas and adrenocortical carcinomas has been observed, probably due to increased use of advanced imaging analysis (CT scan, MRI, ultrasonography), and progression towards use of high-resolution imaging techniques (Table 3.3).[119]

In a 2013 report of adrenocortical carcinomas (n=359, 55% female, age 1-91 years, median age 56 years), in the Netherlands Cancer Registry (1993-2010), incidence appeared to be decreasing over time from 1.3 per million in 1993 to 1.0 per million in 2010. However, the authors suggested that individuals with pre-malignant tumors might have undergone early surgery.[127]

***Age***

The prevalence of adrenal tumors is reported to increase with age (Table 3.4). Pooled studies of deceased individuals estimate the incidence of adrenal incidentalomas to be <1% for age <30 years and 7-10% for age ≥70 years.[116,128] Overall the prevalence is estimated to be 3% of the population at middle-age and up to 10% in the elderly.[116,128,129] In a worldwide literature review (1952-1992, n=1,330) of adrenocortical

**Table 3.3**

**Temporal increase in the prevalence of adrenocortical carcinomas — time of diagnosis of 725 Adrenocortical carcinomas in the SEER database, US.**

| CONDITION | DATA SOURCE | METHOD | POPULATION | TIME PERIOD | PREVALENCE (%) |
|---|---|---|---|---|---|
| Adrenocortical carcinomas | SEER 12 registries database, 1973-2000 | Retrospective study | US, 54.1% females, age 1-97 years, average age at diagnosis 51.2 years (n=725) | 1973-1979 | 14.1 |
| | | | | 1980-1986 | 20.0 |
| | | | | 1987-1993 | 25.9 |
| | | | | 1994-2000 | 40 |

Source: Kebebew et al. 2006[119]

Abbreviations: SEER, Surveillance, Epidemiology, and End Results.

**Table 3.4**

**Incidence rate of adrenocortical carcinomas according to age, US.**

| | | | INCIDENCE OF ADRENOCORTICAL CARCINOMAS PER 100,000 INDIVIDUALS | |
|---|---|---|---|---|
| DATA SOURCE | POPULATION | AGE RANGE (YEARS) | MALE | FEMALE |
| SEER, Cancer statistics review, 1975-2012 | US, age-adjusted, all races | 0-14 | NC | 0.0 |
| | | 15-39 | 0.0 | 0.1 |
| | | ≥40 | 0.2 | 0.3 |

Source: National Cancer Institute[130]

Abbreviations: SEER, Surveillance, Epidemiology, and End Results.

Note: NC, statistic not calculated as rate based on <16 cases.

carcinomas, 62.3% of patients were >30 years of age. Several large series (>50 patients) suggest a bimodal age distribution for peak of incidence (<5 years and at 40-50 years) (Table 3.5).[121]

Pediatric adrenal carcinomas are rare, with an estimated incidence of 0.3 per million children (<15 years) in the US, with ~25 new cases diagnosed each year, representing 0.2% of childhood tumors.[132,133] The main presenting symptoms are hormonal excess (61%), abdominal pain (13%) and abdominal mass (26%).[133] A very significant proportion of adrenocortical carcinoma (50-80%) is associated with TP53 germline mutations and the diagnosis of Li Fraumeni syndrome. Childhood ACC can also occur as part of Beckwith Wiedemann syndrome.[134]

***Tumor Location***

While a left- or right-located adrenal lesion is not linked to any particular disease state, bilateral lesions can indicate metastasis, congenital adrenal hyperplasia, bilateral cortical adenomas, or infiltrative disease.[100] In a prospective evaluation in Italy, Bovio and colleagues

**Table 3.5**

**Peak age of adrenal tumors, worldwide.**

| CONDITION | PEAK AGE (YEARS) | MEAN OR MEDIAN AGE AT DIAGNOSIS (YEARS) | REFERENCES |
|---|---|---|---|
| Adrenal incidentalomas | 40-60 (range) | 55 (mean) | Barzon et al. 2003[101] |
| Adrenocortical carcinomas | <5 | 4 (median) | Fassnacht et al. 2013[118] |
| | 40-50 (range) | 44 (median) | Wajchenberg et al. 2000[131]<br>Wooten et al. 1993[121] |

**Table 3.6**

**Prevalence of adrenal mass location.**

| | | | PREVALENCE OF ADRENAL MASS LESION LOCATION IN PATIENTS (%) | | | |
|---|---|---|---|---|---|---|
| DIAGNOSIS | POPULATION | DATA SOURCE | RIGHT | LEFT | BILATERAL | REFERENCES |
| Adrenocortical carcinomas | Worldwide, females 58.6%, 1952-1992 (n=1891) | Review of English literature from 87 studies | 44.8 | 52.8 | 2.4 | Wooten et al. 1993[121] |
| Adrenal incidentalomas | Worldwide | CT scan, MRI, or ultrasonography (if confirmed by CT scan or MRI) | 50-60 | 30-40 | 10-15 | Anagnostics et al. 2009[100]<br>Barzon et al. 2003[101];<br>Mantero et al. 2000[135] |
| Adrenocortical carcinomas | US, median age 55 years, females 58.2%, 1985-2005 (n=3982) | National Cancer Data Base (NCDB) | 41.3 | 49.6 | 1.1 | Bilimoria et al. 2008[108] |
| Lung cancer metastasis | Italy, adults age 50-79 years, median age 58 years, no adrenal hyperfunction (n=520) | Chest CT scan in a screening program for lung cancer | 26 | 60.8 | 13.2 | Bovio et al. 2006[116] |
| Adrenal incidentalomas | Korea, adults, age 20-86, 55.2% females (n=348) | CT scan, 2005-2012 | 30.2 | 62.0 | 7.8 | Kim et al. 2013[125] |

suggested that the right-side dominance of adrenal tumors in earlier studies may be explained by ultrasonography being less accurate in detecting left-side adrenal masses.[116] More recent imaging with CT and MRI scans shows left adrenal gland tumors to be slightly higher than right adrenal tumors (Table 3.6).[108,116]

***Tumor Size and Stage***

Despite some overlap, adrenal adenomas are generally smaller (usually ≤4cm) than adrenal carcinomas (Table 3.7), with 5-25% of adrenal adenomas increasing in size during follow-up.[101] Reinhard and colleagues analyzed 498 consecutive autopsies in Germany, and identified 0.3-8 mm nodules in 53.7% of cases, and 3.2-28 mm adenomas in 5% of cases.[136] In a large study of adrenal incidentalomas, tumor mass size was the most reliable variable to distinguish adenomas and carcinomas.[135] In a US report of 166 non-functional unilateral benign adrenal incidentalomas identified by CT scan (between 1976 and 1994) in 100% of patients, masses were ≤3cm, while 89% were ≤2cm, and 52% were ≤1cm.[137] Contrary to these findings in benign incidentalomas, adrenocortical carcinomas are larger in size. In a US study of 392 adrenocortical carcinomas, only 4.2% were ≤6cm and in another single center study, only 3% of 391 adrenocortical carcinomas were <5cm.[119,138] In a US SEER database study (1988-2000) of 457 adrenocortical carcinomas compared to 47 benign adrenal tumors, the risk of malignancy increased with tumor size: 52% for tumors ≥4cm, 80% for those ≥6cm, 95% for ≥8cm, and 98% for ≥10cm.[139]

At diagnosis, the majority of adrenocortical carcinomas are already at the advanced stages III and IV (Table 3.8).[119,133,138,140]

***Metastases***

Adrenal masses discovered during abdominal imaging are not generally considered to be adrenal incidentaloma, however, in patients with known malignancies, the risk of an adrenal mass being a metastasis is high (45-73%) and increases with tumor size (43-100% for >3cm tumors). In patients with extra-adrenal malignancies (lung, breast, kidney cancers; melanoma and lymphoma), adrenal metastases were identified in 3-40% at autopsy, and 6-20% of patients in radiological studies.[101] Cancer in an unknown primary site can occasionally involve the adrenal glands, but metastatic cancer presenting as a true incidentaloma is rare. A 1998 US retrospective review of 1,639 cancer patients with an occult primary malignancy identified involvement of the adrenal gland (original site or metastasis) in 5.8% of patients, and tumors solely in the adrenal gland in 0.2% of patients.[141]

***Hormone Excess Syndromes***

Most adrenal incidentalomas are non-functioning, while ~15% show secretion of cortisol, aldosterone or medullary hormones.[101] The most common disorder in incidentalomas (1-29%, average 9%) is the development of autonomous cortisol secretion, which remains subclinical in two-thirds of cases.[101] Less than 1 in every 1000 adrenal masses, originally identified as benign, eventually became malignant, and 1.7% developed hyperfunction, usually involving cortisol.[101] Although most adrenal adenomas are benign and non-functioning, there is still a concern that subclinical levels of autonomous hormone secretion cause metabolic abnormalities, which represent well known risk factors for example cardiovascular morbidity (e.g. hypertension, diabetes, dyslipidemia) (Table 3.9).[142,143]

A study of adrenal incidentalomas (n=94, 1995-2005, Turkey) identified hypertension in 63%, obesity in 55%, diabetes mellitus in 36%, hypercholesterolemia in 36%, and low HDL cholesterol in 36% of cases, with similar frequencies to those in clinical Cushing's syndrome.[144] The risk of autonomous hormone secretion is higher with larger (>3cm) lesions.[101,108] A 2011 report by Muscoguri and colleagues identified a direct correlation between mass size and insulin resistance, and in 2010, Kolanska and colleagues reported a higher prevalence (40%) of obesity in a cohort with non-functioning adenomas than in the general population.[145,146]

A number of worldwide studies indicate a higher prevalence (average 10%; range 6-23%) of subclinical Cushing's syndrome in adrenal incidentalomas.[147] Subclinical Cushing's syndrome is associated with metabolic syndrome, hypertension, and dyslipidemias, but without overt clinical symptoms or signs of Cushing syndrome (Table 3.9).[100,101,103] Patients with subclinical Cushing's syndrome showed increased risks of cardiovascular disease and of developing overt Cushing's disease (12.5% after 1 year).[101,126,148] It was reported to be higher in patients with resistant hypertension (8%, 423 patients, age 1-80 years, Brazil), in young subjects (7.5%, 80 hypertensive patients, age 12-40 years, Romania), and in patients with osteoporosis and vertebral fractures (4.8%),

**Table 3.7**

| Size of tumors in adrenal adenomas and adrenocortical carcinomas, worldwide. | | | |
|---|---|---|---|
| CONDITION | POPULATION | AVERAGE (CM) ±SEM | REFERENCES |
| Adrenal incidentalomas | US, children, age <19 years (n=7) | 3.3 ±0.6 | Hanna et al. 2008[133] |
| | Italy, age 15-86 years (n=1004) | 3.5<br>(range 1-15) | Mantero et al. 2000[135] |
| Adrenocortical carcinomas | US, children, age <19 years (, n=16) | 8.5±1.2 | Hanna et al. 2008[133] |
| | Italy, age 15-86 years (n=1004) | 7.5<br>(range 2.6-25) | Mantero et al. 2000[135] |
| | US, age 1-97 years, average age 51.2 years, 54.1% female, SEER 12 registries database, 1973-2000 (n=725) | 12<br>(range 2-36) | Kebebew et al. 2006[119] |

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; SEM, standard error of mean.

**Table 3.8**

| Adrenocortical carcinoma characteristics, US. | | | | | |
|---|---|---|---|---|---|
| DATA SOURCE | METHOD | POPULATION | CHARACTERISTICS | PERCENTAGE | REFERENCES |
| SEER 12 registries database, 1973-2000, 26% of the US population | Retrospective study | US, adrenocortical carcinomas, 54.1% females, age at diagnosis 1-97 years, average 51.2 years (n=725) | Localized | 40.6 | Kebebew et al. 2006[119] |
| | | | Distant | 34.8 | |
| | | | Regional | 17.9 | |
| | | | Unstaged | 6.7 | |
| | | | Stage I | 19.3 | |
| | | | Stage II | 20.3 | |
| | | | Stage III | 34.3 | |
| | | | Stage IV | 25.9 | |
| Mayo Clinic, review of charts from histologically confirmed cases of adrenocortical carcinomas, | Retrospective review | US, children, avg. age 9 years, female:male 1.9:1, adrenocortical carcinomas, 1976-2005 (n=16) | Stage I | 8 | Hanna et al. 2008[133] |
| | | | Stage II | 13 | |
| | | | Stage III | 4 | |
| | | | Stage IV | 43 | |
| Michigan Endocrine Oncology Repository | Retrospective single-center study | US, adult, female:male 1:1.15, adrenocortical carcinoma, Dec. 1979-Jan. 2013, (n=391) | Stage I | 3 | Else et al. 2014[138] |
| | | | Stage II | 43 | |
| | | | Stage III | 28 | |
| | | | Stage IV | 26 | |

Abbreviations: SEER, Surveillance, Epidemiology, and End Results.

relative to those with secondary hypertension (1%, 4,429 patients at a hypertension referral center, US).[147,149-151] However, not all of the patients in these studies had a proven adrenal mass, but rather biochemical evidence for some degree of autonomous cortisol production. In the hypertensive population, the prevalence of primary hyperaldosteronism is estimated to be up to 10%; (60% of which is caused by aldosterone-producing adenomas).

Primary aldosteronism is a diverse group of adrenal disorders, usually arising due to either sporadic aldosterone-producing adenoma (Conn adenoma or aldosteronoma) or sporadic uni- or bilateral adrenal hyperplasia, and very rarely as familial form of bilateral adrenal hyperplasia.[115] In primary aldosteronism, the adrenal gland produces aldosterone in an autonomous fashion, resulting in secondary hypertension with detrimental effects on the cardiovascular and renal systems.[107,153-155] Even moderate increases in aldosterone are implicated in increased cardiovascular morbidity and mortality.[156] Studies indicate that aldosterone-producing adenomas exist in 3.3-11.2% of the hypertensive population.[153,157] Conn adenomas represent ~30-60% of the primary aldosteronism population.[158] Mulatero and colleagues reported a higher risk for cardiovascular events in aldosterone-producing adenoma patients compared to patients with essential hypertension. During follow-up, aldosterone-producing adenoma patients had more strokes and arrhythmias and a higher percentage developed type-2 diabetes than did patients with essential hypertension.[159]

***Mutations***

Table 3.10 presents data on the prevalence of somatic mutations associated with aldosterone-producing adenomas (Conn's adenoma). Another cause of primary aldosteronism is bilateral adrenal hyperplasia, which can arise sporadically or in the setting of germline

**Table 3.9**

**Prevalence of co-morbidities in non-functioning adrenal adenomas and sub-clinical Cushing's syndrome, worldwide.**

| CO-MORBIDITIES | PREVALENCE OF CO-MORBIDITIES IN NON-FUNCTIONING ADRENAL ADENOMAS (%) (Muth et al. 2013[152]) | PREVALENCE OF CO-MORBIDITIES IN SUBCLINICAL CUSHING'S SYNDROME (%) (Barzon et al. 2003[101] and Anagnostis et al. 2009[100]) |
|---|---|---|
| Hypertension | 48 | 40-90 |
| Cardiovascular disease | 23 | N/A |
| Diabetes/glucose intolerance | 9 | 25-75 |
| Hyperlipidemia | 12 | 50 |
| Osteopenia | N/G | 40-50 |
| Osteoporosis | 5 | N/A |
| Obesity | 40 | 35–50 |

Abbreviations: N/G, not given; N/A, not available.

**Table 3.10**

**Prevalence of the most common somatic mutations causing aldosterone-producing adenoma.**

| DATA SOURCE | POPULATION | MUTATION | PREVALENCE IN PATIENTS WITH ALDOSTERONE-PRODUCING ADENOMA (%) |
|---|---|---|---|
| European Network for the Study of Adrenal Tumors | Patients across 7 centers (n=474) | all somatic mutations | 54 |
| | | *KCNJ5* | 38 |
| | | *CACNA1D* | 9.3 |
| | | *ATP1A1* | 5.3 |
| | | *ATP2B3* | 1.7 |

Source: Zennaro et al. 2015[160]

mutations.[160] Table 3.11 summarizes prevalence data of the different types of adrenal hyperplasia and their associated mutations.

In one study *TP53* germline mutations were found in 67% of individuals with adrenocortical carcinoma (n=21), of which 80% were children (<18 years).[161] In a German report the *TP53* mutation was identified in 3.9% of Caucasians with adult-onset adrenocortical carcinoma.[162] In a US series, the prevalence of *TP53* mutations was 5.8% in the adult population.[163] The prevalence of the *TP53* germline mutation R337H was reported to be 15-times higher (0.3%) in children in southern Brazil than other areas, with prevalence of 97% in childhood adrenocortical tumors.[118,164,165]

Li-Fraumeni syndrome is rare, autosomal dominant cancer disorder often caused by gene mutations that inactivate the tumor suppressor *TP53* gene. Li-Fraumeni syndrome patients are at high risk of developing different types of cancers including breast, bone, brain and adrenal cancer (Table 3.12). Another fairly prevalent syndrome in adrenal cancer patients is Lynch syndrome, which is responsible for 3-5% of all adrenal cancers.[163] Individuals with Beckwith-Wiedemann Syndrome are at a high risk of developing cancers of the liver, kidney and occasionally the adrenal cortex. Described as a complex of myxomas, spotted skin pigmentation and endocrine overactivity, Carney complex, caused by *PRKAR1A*, is a multiple neoplasia syndrome, mostly associated with micronodular hyperplasia. Two cases of adrenal cancer have also been described.[166-168] Germline mutations in a related gene, *PRKACA* has been found mutated in patients with adrenal hyperplasia, and somatic mutations are found in 30% of cortisol-producing adenomas.[169]

## 3.2 COST BURDEN OF DISEASE

In the treatment of primary aldosteronism, some clinicians advocate oral therapy with mineralcorticoid-receptor antagonists to be more cost-effective than operative resection, while others have determined that surgery is more cost-effective than a pharmacological approach (Table 3.13). Based on 2009 treatment costs, a laparoscopic adrenalectomy in a hospital setting is expected to cost $8,378.63.[114] The authors estimated that if adrenalectomy costs rose 2.5-fold to $22,524.59, or the cost of selective venus sampling quadrupled from $2,171 to $9,041, or the surgical failure in improving blood pressure increased six-fold to affect 32% of patients, then the pharmacological option would be the least costly strategy. However, treatment costs vary significantly, even within the US, and there is no conclusive study suggesting a cost-benefit of strategy, surgery or pharmacotherapy.

## 3.3 DEMOGRAPHIC DIFFERENCES

In a literature review of 6 worldwide studies (n=71,206), no overall sex differences in incidentalomas were identified at autopsy.[101] However, two studies reported a high female-to-male ratio in adrenal masses.[101,174] Both studies hypothesized that the increased incidence in females could be entirely due to the higher rates of abdominal scans in females than males (Table 3.14).[101,103] Barzon

**Table 3.11**

Subtypes of adrenal hyperplasia and associated mutations, worldwide.

| SUBTYPE OF ADRENAL HYPERPLASIA | DATA SOURCE | POPULATION | ASSOCIATED GERMLINE MUTATIONS | HORMONE SECRETED | REFERENCES |
|---|---|---|---|---|---|
| Macronodular adrenal hyperplasia | Not stated | Not stated | *ARMC5, PDE11A, PDE8B, PRKACA* | Cortisol | Louis et al. 2014[170] |
| Familial hyperaldosteronism-I (FH-I) | University of Turino, Italy | Primary aldosteronism diagnosis (n=300) | *CYP11B2/CYP11B1* chimera | Aldosterone under adrenocorticotropic hormone control | Mulatero et al. 2011[171] |
| Familial hyperaldosteronism-II (FH-II) | | | Genetic linkage to chromosome #7p22, but mutations(s) unknown | Aldosterone | |
| Familial hyperaldosteronism-III (FH-III) | | | *KCNJ5* | Aldosterone | |

**Table 3.12**

**Hereditary syndromes associated with adrenocortical carcinoma.**

| SYNDROME | PREVALENCE IN PATIENTS | PREVALENCE IN GENERAL POPULATION | GENE MUTATION | REFERENCES |
|---|---|---|---|---|
| Li-Fraumeni syndrome | 3-6% of adults with adrenocortical carcinoma; 50–80% of children with adrenocortical carcinoma | 1:20,000 to 1:1,000,000 | *TP53* | Fassnacht et al. 2013[118]; Wasserman et al. 2015[134] Raymond et al. 2013[163]; Else et al. 2014[122] |
| Multiple endocrine neoplasia type 1 (MEN1) | 1–2% of adults with adrenocortical carcinoma | 1:30,000 | *MENIN* | Else et al. 2014[122] |
| Lynch syndrome | 3.2% of adults with adrenocortical carcinoma | 1:440 | *MSH2; MSH6; MLH1; PMS2* | Raymond et al. 2013[163] Else et al. 2014[122] |
| Beckwith-Wiedemann syndrome | Very rare, only found in children with adrenocortical carcinoma | 1:13,000 | *IGF2; H19*; *CDKN1C* (*gene* locus 11p15) | Else et al. 2014[122] |
| Familial adenomatous polyposis | Very rare: <1% of adults with adrenocortical carcinoma | 1:30,000 | *APC* | Else et al. 2014[122] |
| Carney complex | Very rare (2 case reports) in adrenocortical carcinoma. | More than 700 patients worldwide | *PRKAR1A* | Else et al. 2014[122]; Kirschner et al. 2000[172] Anselmo et al. 2012[167]; Morin et al. 2012[173] |

**Table 3.13**

**Comparison of discounted expected costs of two treatment regimes for aldosterone-producing adenoma in primary hyperaldosteronism.**

| METHOD | POPULATION | TREATMENT | COST ($) |
|---|---|---|---|
| Markov state transition model | 40-year old (female) reference patient with 41 years of life remaining | Endocrine Society's Practice Guidelines: selective venus sampling and laparoscopic adrenalectomy | 27,821 |
| | | Long-term pharmacological therapy: (daily spironolactone at $219 annually, plus eplerenone in 52% of cases) with 48% success of controlling hypertension, 46.9% of improving blood pressure but still requiring a single hypertensive | 34,691 |

Source: Reimel et al. 2010[114]

Note: The cost estimates are based on 2009 US treatments costs. All cost estimates included physician's visits, laboratory radiologic evaluation, medications, procedures, Medicare costs, and reimbursement but excluded costs outside the healthcare system (transporation, lost-productivity). Only costs that differed between the two treatment regimens were included.

**Table 3.14**

**Female-to-male sex ratios in adenomas and adrenocortical carcinoma.**

| DATA SOURCE | METHOD | POPULATION | CONDITION | OVERALL FEMALE: MALE SEX RATIO | REFERENCES |
|---|---|---|---|---|---|
| Literature review | Literature reviews | n=71,206 | Adenomas at autopsy | *1.0* | Barzon et al. 2003[101] |
| Literature reviews | Literature reviews | Adrenal lesions | Adenomas | *1.2-1.6* | Barzon et al. 2003[101]; Di Dimalzi et al. 2014[175]; Audenet et al. 2013[174]; Mantero et al. 2000[135] |
| International Pediatric Adrenocortical Tumor Registry, 1990-2001 | Descriptive analysis | US, children, age <20 years (60% <4 years, 14% >13 years); 61.4% female (n=254) | Childhood adrenocortical tumors | Overall: 1.6<br>Age <4 years: 1.7<br>Age 4-12 years: 0.8<br>Age ≥13 years: 6.2 | Michalkiewicz et al. 2004[176] |
| 1976-2005 | Retrospective review | US, children, age <19 years, average age 9.0 ±1.6 years (n=23) | Childhood adrenocortical carcinomas n=16), and adenomas (n=7) | 1.9 | Hanna et al. 2008[133] |
| SEER 12 registries database, 1973-2000 | Retrospective study | 54.1% females, age 1-97 years, average age at diagnosis 51.2 years US, (n=725) | Adrenocortical carcinoma | 1.2 | Kebebew et al. 2006[119] |
| International Pediatric Adrenocortical Tumor Registry, 1990-2001 | Descriptive analysis | US, children <20 years, (n-254) | Adrenocortical carcinoma (pediatric) | 1.6 | Michalkiewicz et al. 2004[176] |
| Endocrine Department of the Hospital Cochin, 1963-1987 | Retrospective study | France, n=105, females n=75, mean age 46 years, range 6-81 years | Adrenocortical carcinomas | 2.5 | Luton et al. 1990[177] |
| Michigan Endocrine Oncology repository, diagnosed December 1979 to January 2013 | Retrospective single-center study | US, n=391 | Adrenocortical carcinomas | 1.5 | Else et al. 2014[138] |

Note: The cost estimates are based on 2009 US treatments costs. All cost estimates included physician's visits, laboratory radiologic evaluation, medications, procedures, Medicare costs, and reimbursement but excluded costs outside the healthcare system (transporation, lost-productivity). Only costs that differed between the two treatment regimens were included.

and colleagues also reported an increase in prevalence of autopsy incidentalomas with age: 0.2% in young patients and 6.9% in patients of age >70 years.[101] In adults with adrenocortical carcinomas, a lower median age-at-diagnosis was reported for females vs. males (30 vs. 39 years). In males, adrenocortical carcinoma tumors were found more often in patients age >30 years (71.7%) than age <30 years (28.4%).[121] In several studies, adrenocortical carcinoma (n=1891) is more common in females than males with a ratio of 1.5:1.[121,138]

No significant differences were identified in the incidence of adrenocortical carcinoma between races.[130]

3.4

## LIFE EXPECTANCY AND MORTALITY

Autonomous cortisol production bears an increased mortality in patients with adrenal incidentalomas. In one study analysing 206 patients, 18 patients had died and of these 17 had cortisol level >1.8 μg/dL.[178] No statistics on mortality were available for nodular hyperplasias or adrenal familial hyperplasias. However, Li and Yang reported that in a retrospective review of 23 cases of bilateral adrenal macronodular hyperplasias (and the associated Cushing's syndrome) in China, 20 showed elevated cortisol levels (associated with high morbidity and mortality).[179] Zenarro and colleagues stated that familial hyperaldosteronism-I (in France) was associated with hypertension from an early age (family history of hypertension <50 years, history of hypertension <20 years, hypertension that is difficult to control), resulting in high morbidity and mortality at an early age.[160]

Adrenocortical carcinoma is a malignancy with a poor prognosis with median 5-year survival rates (range 25-54%).[176,180] Data from a number of studies suggests that tumor size does not appear to correlate with metastatic disease or survival.[108,180,181] In a 2008 review by Bilimoria and colleagues of 3,982 adrenocortical carcinoma cases diagnosed between 1985 and 2005 in the US, survival was significantly diminished with increasing age (>55 years), high-grade tumors (HR, 2.26), incomplete surgery (HR, 2.06), nodal metastases (HR, 1.56), distant metastasis (HR, 2.20), or in patients who had undergone surgery with resection of a contiguous organ (HR, 1.23).[108] Microscopically complete resection was associated with lower recurrence rates in a 2013 study.[182] Several studies also showed that disease stage correlated with poor outcomes.[122,138,176,183] Table 3.15 presents the relationship between disease stage and median survival.

In a US study of 3,982 adrenocortical carcinomas, 26.5% of patients had nodal metastasis and 21.6% had distant metastasis. The 5-year survival for patients who had undergone resection was 38.6% (median 31.9 months).[108] The risk of death was higher in older patients (>55 years), high-grade tumors (HR, 2.3), involved margins (HR, 2.1), nodal (HR, 1.6) or distant metastasis (HR, 2.2), or surgery with resection of a contiguous organ (HR, 1.2).[108] Distant metastasis was mostly found in liver, lung and bone in 10.9%, 9.0% and 3.1% of cases, respectively.[108] The adjusted HR for death increased with age: 1.0, 1.1, 1.5 and 2.3 for age 18-35 years, 36-55 years, 56-75 years, and >75 years respectively; and the 5-year observed survival rate decreased with age 14.6%, 42.1%, 35.8%, and 23.7% respectively.[108] In a Netherlands study of adrenocortical carcinoma patients, the survival time decreased with advanced disease stage (Table 3.16). The relative-survival decreased with increasing age-at-diagnosis (5-year survival: 44% 0-44 years, 36% 45-59 years, 23% 60-74 years, and 37% >75 years).[108]

In pediatric adrenal tumors, complete tumor excision was associated with significantly better outcome. Outcome for ACC was better at earlier disease stages (Table 3.17).[133]

3.5

## KEY TRENDS AND HEALTH OUTCOMES

Surgery is the mainstay of treatment for carcinomas and most hormone producing adrenal adenomas. Laparoscopic adrenalectomy (first described in 1992) is preferred over open adrenalectomy for small-to-medium size (<8cm), benign, functioning and non-functioning adrenal tumors.[184] Tumors with a presurgical suspicion for adrenocortical carcinomas are best approached with an open adrenalectomy, following oncological principles. In two US studies comparing the two surgeries, the recurrence rate was 86% in 156 adrenocortical carcinoma patients who had undergone open adrenalectomy and 100% in 6 patients who had undergone laparoscopic adrenalectomy, although 2 other studies suggested there was no significant difference between the two surgeries at Stages 1 and 2.[122] Contraindications for laparoscopic adrenalectomy include large benign tumors (>8 cm) and adrenocortical carcinomas. Robot-assisted adrenalectomy (introduced early 2000s) is becoming increasingly popular as it can overcome technical limitations of laparoscopic adrenalectomy, and is shown to consistently reduce blood loss during and after surgery. In a 2011 report from Italy of cortical adenomas (n=19), aldosteronomas (n=2), hyperplasias (n=2), adrenal carcinoma (n=1), others

Table 3.15

**Adrenocortical carcinoma disease stage and median survival times, US.**

| DATA SOURCE | METHOD | POPULATION | STAGE | MEDIAN OVERALL SURVIVAL TIMES (YEARS) | REFERENCES |
|---|---|---|---|---|---|
| Adrenocortical carcinoma patients, University of Texas MD Anderson Cancer Center, 1998-2011 | Retrospective review, 2013 | Age 0-86 years, median age at diagnosis 48.5 years, 3.6% age <18 years, 85% Caucasian, 64.2% female (n=330) | I | 24.1 | Ayala-Ramirez et al. 2013[183] |
| | | | II | 6.08 | |
| | | | III | 3.47 | |
| | | | IV | 0.89 | |
| Adrenocortical carcinoma patients, Michigan Endocrine Oncology repository, diagnosed December 1979 to January 2013 | Restrospective single-center study | Adults age >16 years, mean age at diagnosis 47.4 years, 86% Caucasian male:female ration 1:1.5 (n=391) | I | 4.77 | Else et al. 2014[138] |
| | | | II | 6.14 | |
| | | | III | 2.50 | |
| | | | IV | 1.12 | |

Table 3.16

**Survival in months for adrenocortical carcinoma patients according to disease stage, Netherlands.**

| DATA SOURCE | POPULATION | ADRENOCORTICAL CARCINOMA DISEASE STAGE | MEDIAN SURVIVAL, MONTHS (RANGE) |
|---|---|---|---|
| Netherlands Cancer Registry 1993-2010 | Netherlands, 55% female, age 1-91 years, median age 56 years (n=359) | I-II (33%) | 159 (93-225) |
| | | III (10%) | 26 (4-48) |
| | | IV (35%) | 5 (2-7) |

Source: Bilimoria et al. 2008[108]

Note: 22% had unknown disease stage; Stage I-II: carcinoma in situ or localized in tissue of origin; Stage III: tumor infiltration into surrounding tissue or at least 1 positive lymph node or tumor infiltration into surrounding tissue and at least 1 positive lymph node; Stage IV: presence of distant metastasis.

Table 3.17

**Survival rates in pediatric adrenal tumors, US.**

| DATA SOURCE | METHOD | POPULATION | DISEASE CHARACTERISTICS | 5-YEAR SURVIVAL RATE | REFERENCES |
|---|---|---|---|---|---|
| Pediatric adrenocortical tumors examined by histology Mayo Clinic 1976-2005 | Retrospective analysis | US, children age 34 days-19 years, mean age 9 years, 15 females, 8 males, n=7 adenomas, n=16 adrenocortical carcinomas (n=23), all >2.5cm | Excised adenomas | 100% | Hanna et al. 2008[133] |
| | | | Excised adrenocortical carcinomas | 34% | |
| | | | **Adrenocortical carcinomas stages I and II:** | | |
| | | | 5-year survival | 100% | |
| | | | **Adrenocortical carcinomas stages III and IV:** | | |
| | | | 5-year survival | 0% | |
| | | | Median survival | 21 months | |
| Pediatric adrenocortical tumors, International Pediatric Adrenocortical Tumor Registry, 1990-2001 | Descriptive analysis | US, children <20 years, (n-254), overall male:female ratio 1:1.6, vitrilization in 84.2%, Cushing's syndrome without viriization 5.5%. Tumors completelyresected in 83%. Disseminated/residual disease treated with mitotane, cisplatin, etopside, and/or doxorubicin, or radiation therapy. Median follow up 2 years 5 months. | Survived without evidence of disease (follow-up of 2 years 5 months) | 61.8% | Michalkiewicz et al. 2004[176] |
| | | | Died (Follow-up of 2 years 5 months) | 38.2% | |
| | | | 5-year event-free survival estimate | 54.2% (48.2-60.2%) | |

(n=18); robot-assisted adrenolectomies led to minimal blood loss (median 27ml) and short operative times (118±46 mins). Differences in surgery time between right and left side (125 min vs. 110 min) and blood loss (86 ml vs. 35 ml) were not statistically significant.[185] In a 2014 retrospective study (n=76, 2000-2010) of US medical charts by Brandao and colleagues, a significantly lower surgery-related blood loss was reported for robot-assisted adrenolectomies than for laparoscopic adrenalectomy (median 50ml vs. 100ml) performed by the same surgeon, but the authors identified no significant differences in the length of hospital stay.[186]

A 2008 study by Brunaud and colleagues, reported operating times were determined by the surgeon's experience; the longer operation times with robot-assisted adrenalectomies compared with laparoscopic adrenalectomy did not apply after a surgeon's learning curve of 20 cases. The mean operating time in laparoscopic adrenalectomies was higher in obese patients (body mass index >30 kg/m2) than those with a lower BMI (90 vs. 78 min respectively), and for patients with tumor size >5.5cm, than those with smaller tumors (100 vs. 80 min, respectively). These difference did not apply to robot-assisted adrenalectomies.[187]

In a 4-study review of robot-assisted adrenalectomies, the morbidity rate was 0-20% and the mortality rate was 0%; in a single study for laparoscopic adrenalectomy, the reported mortality rate was 0%.[185] From a review of 100 laparoscopic adrenalectomies from 19 publications, the most commonly reported complications of surgery were bleeding (40%) and injury to peritoneal and retroperitoneal organs (4.2%), with an overall mortality rate of 0.2% 30 days post surgery (0.8-1.2% deaths in 4 centers, and zero deaths in 15 centers).[184,188] Bilateral surgery can lead to higher blood loss, higher mortality (4/7 deaths) and lower success rates of disease management (50-100%) than unilateral adrenalectomies, which can achieve endocrinolgical cure.[188]

***Non-functioning adrenal incidentalomas***

Conservative management is recommended over surgery in cases of stable non-functioning adrenal incidentalomas that lack autonomous hormone production. A quality-of-life survey of non-functioning adrenal incidentaloma patients (released from surveillance after 24 months of stable disease) found that although the follow-up program was well tolerated, 30% of cases showed signs of depression, possibly related to the significant hypertension and metabolic co-morbidities, as outlined earlier in Table 3.9.[152]

***Conn's syndrome***

Complication rates for aldosterone-producing adenomas are reported to be 7%.[184,188] Post-surgery studies of laparoscopic adrenalectomies for Conn's syndrome showed 95-100% success in achieving normokalaemia, with hypertension cured or significantly improved in 88-100% of surgeries.[188] Persistant hypertension was reported in 0-12% of patients post-adrenalectomy.[184] A worldwide review of 13 studies with respect to outcome of laparoscopic adrenalectomies is shown in Table 3.18.

***Subclinical Cushing's syndrome***

Subclinical Cushing's syndrome is detected at low rates in the course of surveillance of non-functioning adrenal adenomas. In a retrospective study of conservatively managed non-functioning adrenal incidentalomas, Morelli and colleagues reported that 8.2% of patients progressed to subclinical Cushing's syndrome during 5 years of follow-up.[189] Giordano and colleagues reported this to be the case in just 5.1% of patients.[102]

**Table 3.18**

Patient outcome after laparoscopic adrenalectomies in aldostereronoma, worldwide.

| CONDITION | POPULATION | PROCEDURES | OPERATING TIME (MINUTES) MEAN (RANGE) | BLOOD LOSS (MILLILITERS) MEAN (RANGE) | LENGTH OF STAY (DAYS) MEAN (RANGE) |
|---|---|---|---|---|---|
| Aldosteronomas or Conn's syndrome | Review of 13 worldwide studies (n=323) | Laparoscopic adrenalectomies | 164 (38-295) | 177 (35-297) | 3.4 (1-10.4) |

Source: Gumbs and Gagner. 2006[184]

In 2014 Morelli and colleagues reported that at diagnosis, patients with subclinical Cushing's syndrome had higher rates of diabetes mellitus and cardiovascular incidents than patients without subclinical Cushing's syndrome. After a 5-year follow-up, subclinical Cushing's syndrome correlated with worsening metabolic symptoms and cardiovascular incidents.[189] These studies contradicted data from Giordano and colleagues, who reported finding no differences in hypertension and metabolic diseases between non-functioning adrenal incidentalomas and subclinical Cushing's syndrome.[102]

While some studies recommend simply monitoring subclinical Cushing's syndrome, others suggest the higher prevalence of cardiovascular disorders warrants surgery in both subclinical Cushing's and non-functioning tumors, especially in patients exhibiting hypertension, obesity, and diabetes.[144] A study of 45 subclinical Cushing's syndrome cases, by Toniato and colleagues, reported that surgery relieved hypercortisolism and co-morbidities (Table 3.19); while conservative management only led to a worsening of certain conditions (diabetes mellitus, hypertension, hyperlipidemia).[190] The improvement in comorbidities post surgery from another study, a systemic review by Iacobone and colleagues, are also shown in Table 3.19.[191] However, subclinical Cushing's syndrome poses a particular challenge as there is no consensus, whether it needs to be treated or whether treatment of co-morbidities is favorable.

### *Adrenal hyperplasia*

Macronodular adrenal hyperplasia can present with or without hormone excess; patients with hypercortisolism can present with subclinical Cushing syndrome or clinical Cushing syndrome. Unilateral adrenalectomy addressing the larger adrenal gland is often the treatment of choice and often normalizes the clinical symptoms.[179] Familial macronodular adrenal hyperplasias with a predisposition to cortisol production is caused by *ARMC5* mutations in a significant number of patients. Adrenocortical hyperplasias can also lead to primary aldosteronism, particulalrly in the setting of *KCNJ5* germline mutations. However, sporadic hyperplasia of the zona glomerulosa is rarely evident on imaging, but can be observed

**Table 3.19**

**Percent improvement in subclinical Cushing's syndrome co-morbidities with surgery or conservative management.**

| | PERCENTAGE IMPROVEMENT IN COMORBIDITIES IN SUBCLINICAL CUSHING'S SYNDROME PATIENTS (%) | |
|---|---|---|
| CO-MORBIDITIES | LAPAROSCOPIC ADRENALECTOMIES PERFORMED OVER A 15-YEAR PERIOD BY THE SAME SURGEON, N=45 (Toniato et al. 2009[190]) | SYSTEMATIC REVIEW, MEDLINE, EMBASE AND COCHRANE DATABASES (1980-2013) SEARCHED FOR OUTCOMES OF UNILATERAL ADRENALECTOMY; 7 PAPERS, 6 RETROSPECTIVE STUDIES, 1 CLINICAL TRIAL, N=230 (Iacobone et al. 2015[191]) |
| Diabetes Mellitus | 62.5 | 46 |
| Hypertension | 67 | 72 |
| Hyperlipidemia | 37.5 | Inconclusive |
| Obesity | 50 | 29 |
| Osteoporosis | No change | No change |

**Table 3.20**

**Detection of adrenocortical carcinomas, US.**

| DATA SOURCE | METHOD | POPULATION | DETECTION METHOD | PERCENTAGE OF ADRENOCORTICAL CARCINOMAS DETECTED (%) |
|---|---|---|---|---|
| University of Michigan Health Systems, over 10 years | Retrospective review | Adrenocortical cases | Incidental CT scan | 20–30 |
| | | | Increased adrenal hormone production: | 45–70 |
| | | | Cortisol | 50–80 |
| | | | Androgens | 40–60 |
| | | | Cortisol and androgens | 50 |

Source: Else et al. 2014[122]

microscopically. If untreated, adrenal hyperplasias with primary aldosteronism results in the early onset of hypertension and cerebral hemorrhage.[192] Untreated familial hyperaldosteronism also results in left ventricular hypertrophy.[192,193]

Surgery for sporadic unilateral hyperplasia causing primary aldosteornism usually reduces hypertension and improves cardiovascular outcomes, similar to aldosterone-producing adenomas. Bilateral disease requires pharmacological management.[155,192]

***Adrenocortical carcinoma***

More adrenocortical carcinomas are detected as a result of increased adrenal hormone production rather than as an incidental finding on a CT scan (Table 3.20).[122] The mainstay of a curative approach for ACC is complete oncological surgery, with consideration of an open surgical approach.

The adrenolytic medication, Mitotane, is used as standard care in advanced adrenocortical carcinomas. The first-line therapy for metastatic cancer includes Mitotane with etoposide, doxorubicin and cisplatin.[118] Mitotane has been shown to improve 5-year survival rates in several studies (Table 3.21).[122,180]

Radiation therapy improves local control, but has not been shown to significantly improve survival times.[194] Furthermore, it is recommended that radiation not be used when *TP53* mutations are present.[122]

A study by Fassnacht and colleagues, argued for specialized centers with multidisciplinary teams for treatment and follow-up of adrenocortical carcinoma patients.[122,195] Adrenocortical carcinoma patients appear to have better outcomes when patients are treated at specialized centers.[195]

# IV FAMILIAL NEOPLASIA SYNDROMES

Endocrine neoplasia syndromes are inborn conditions predisposing to the development of one or more endocrine tumors, either benign or malignant.[196,197] In addition, endocrine tumors can also be part of other hereditary syndromes, primarily dominated by non-endocrine neoplasias. On the other hand, sporadic disease is diagnosed in the absence of: pathogenic predisposing mutation, a family history, or syndromic features.[198]

Multiple endocrine neoplasia (MEN) syndromes are characterized by tumors in multiple endocrine organs (Table 4.1).[197] All core endocrine tumor syndromes are inherited in an autosomal dominant fashion. The specific gene mutations and the primary characteristics associated with hereditary neoplasia syndromes are shown in Table 4.1.

## 4.1 PREVALENCE AND INCIDENCE

### 4.1.1 Multiple Endocrine Neoplasia syndromes

Each MEN syndrome subtype is characterized by a number of specific endocrine cancers, and their prevalence is presented in Table 4.2. Approximately 75-95% of MEN1 is due to a genetic mutation in the *MEN1* gene.[197]

### 4.1.2 Pheochromocytoma (PHEO) and Paraganglioma (PGL) syndromes

Between 25% and 52.8% of PGL/PHEO cases are linked to germline mutations causing hereditary PGL/PHEO.[199,202-204] Approximately 2-7% of patients with NF1 develop catacholmine-secreting tumors, usually solitary, benign, adrenal PHEO.[205,206] VHL-associated tumors, are often bilateral and are most often benign, but can be malignant.[202,205,207] The prevalence of diseases associated with PGL and PHEO syndromes are shown in Table 4.3. The most common of these are *SDHx*-related hereditary PGLs.

In 190 PHEO/PGL cases (1993-2008), germline or somatic mutations in one of the major PHEO/PGL-associated genes were identified in 45.5% of the tumors. Germline mutations were identified in 57 patients (13.2% *VHL*, 11.6% *SDHA-D*, 4.7% *RET*, 4.7% *NF1*, 0.5% *TMEM127*).[215]

Due to the high levels of familial cases among apparently sporadic tumor cases, genetic counseling and testing in all cases of PHEO or PGL is recommended. In 2002 it was estimated that up to 24% of apparently sporadic cases could have germline mutations.[216] In 2016, Patocs and colleagues reported that 1 of 15 gene mutations could be present in up to 30% of apparently sporadic PHEO/PGL cases.[217]

**Table 3.21**

| Recent studies of adrenocortical carcinoma treatments, risk factors, and outcomes. | | | | |
|---|---|---|---|---|
| YEAR | DATA SOURCE | POPULATION | RESULTS | REFERENCES |
| 2014 | Prospective study: does tumor size predict outcome | n=37 patients with tumors >8 cm (n=207) | Tumor size not predictive of outcome; 5-year survival rate 25% vs. 50% with addition of Mitotane | Abdel-Aziz et al. 2014[180] |
| 2013 | National Cancer Database: impact of tumor size | Patients with staging information, 1985-2000 (n=2,248) | Tumor size not predictive of metastasis and does not correlate with survival. However, patient age was a predictor of overall survival after resection. | Canter et al. 2013[181] |
| 2014 | Review of 8 retrospective studies, 1989 -2010 | Advanced adrenocortical carcinoma; patients without mitotane (n=527); patients with mitotane (n=212) | Mitotane as adjuvant therapy in 8 studies: disease-free survival was significantly better in 2 studies, not significant in 4, favorable in 1, and significantly worse in 1 study. Overall survival was significantly better/favorable in 1 study.122 | Else et al. 2014[122] |
| 2014 | Review of 10 studies (3 prospective and 7 retrospective), 1984-2007 | Advanced adrenocortical carcinoma; 359 patients; 102 responders | Mitotane as a therapeutic agent (nonadjuvant): all 10 studies showed some cases of partial remission (n=73), stable disease (n-14) and complete remission (n=15) were reported in 3 studies each. | Else et al. 2014[122] Ayala-Ramirez et al. 2013[183] |
| 2013 | Retrospective single center: clinical outcomes | Median age 48.5 (n=330) | For surgical resection median local recurrence time 1.04 years. Median survival 3.21 years. Poor survival: older age, functional tumors; higher disease stage | |
| 2013 | Retrospective cohort, single center study: impact of adjuvant radiotherapy on adrenocortcal carcinomas post surgery | US, 16 received radiation therapy, 32 did not; 1998-2011 (n=48) | Radiation therapy did not improve outcomes after initial surgery. Local recurrence in 43.8% receiving radiation therapy vs. 31.3% in control group. At 5-year, local recurrence rate 53% in radiation therapy group and 67% in non-radiation therapy group. | Habra et al. 2013[194] |
| 2013 | Retrospective study German Adrenocortical Carcinoma Registry: Survival | n=101 who underwent repeated surgery, of which 99 received additional therapies post-surgery | 94% experienced progression (median 6 months); shorter progression-free-survival if both (i) time to first recurrence was >12 months and (ii) microscopically complete resection of recurrent tumors (n = 22; median progression-free-survival 24 months; median overall survival >60 months). | Erdogan et al. 2013[182] |
| 2010 | Single center prospective study for stage II at specialized center | Adults, Stage II (n=149) | Prospective follow-up group (n=30): 30% recurrence rate; 5-year survival 96%; risk of death HR, 0.19. Retrospective group (n=119): 74% recurrence rate, 5-year survival 55%; risk of death HR, 0.03-1.39. Overall 5-year survival in study 58% (n=149). | Fassnacht et al. 2010[195] |
| 2004 | Worldwide Pediatric Adrenocortical Tumor Registry | Age <20 years (n=254) | 5-year survival 54.2%. Disease stage, endocrine dysfunction and age correlated with poor prognosis | Michalkiewicz et al. 2004[176] |

Table 4.1

| Primary characteristics and genetic mutations linked to familial neoplasia syndromes. | | | |
|---|---|---|---|
| FAMILIAL ENDOCRINE NEOPLASIAS | PRIMARY CHARACTERISTICS | GENETIC MUTATIONS | REFERENCES |
| **MEN1 (Wermer's syndrome)** | | | |
| Multiple endocrine neoplasia type 1 (MEN1) | Parathyroid four gland hyperplasia, entero-pancreatic neuroendocrine tumors and pituitary adenoma | *MEN1* | Thakker. 2014[197]; Almeida and Stratakis. 2010[199] |
| **MEN2 (Sipple syndrome)** | | | |
| Familial medullary thyroid carcinoma (FMTC)** | Medullary thyroid carcinoma | *RET* | Lee and Pellegata. 2013[200]; Thakker. 2014[197]; |
| Multiple endocrine neoplasia type 2 (MEN2), also known as type 2A (MEN2A) | Medullary thyroid carcinoma, PHEO, and parathyroid adenoma | *RET* | Thakker. 2014[197]; Almeida and Stratakis. 2010[199] |
| **MEN2B** | | | |
| Multiple endocrine neoplasia type 2B | Medullary thyroid carcinoma, and PHEO | RET | Thakker. 2014[197]; Almeida and Stratakis. 2010[199] |
| **CDKN1B-related MEN*** | | | |
| CDKN1B-related MEN | Parathyroid adenoma, Pituitary adenoma, reproductive organ tumors, and adrenal tumors | *CDKN1B* | Thakker. 2014[197]; Marinoni and Pellegata. 2011[201] |
| **Neurofibromatosis Type I (NF1) (von Recklinghausen disease) and von Hippel-Lindau (VHL) disease** | | | |
| NF1 | PHEO, and extra-adrenal PGL, neural sheath tumors, neurofibromas, and other manifestations | *NF1* | Almeida and Stratakis. 2010[199] |
| VHL | PHEO, pNET, RCC, HBL | *VHL* | |

Abbreviations: PHEO, Pheochromocytoma; PGL, Paraganglioma.

Note: *, Insufficient numbers to estimate penetrance; **, Familial medullary thyroid cancer (FMTC) can either occur alone or as part of the MEN2 phenotype.

Table 4.2

| Prevalence of cancers in Multiple Endocrine Neoplasia (MEN) syndromes, literature reviews, worldwide. | | | |
|---|---|---|---|
| MULTIPLE ENDOCRINE NEOPLASIA SUBTYPE | ENDOCRINE CANCER | LIFE-TIME RISK (%) | REFERENCES |
| MEN1 | Parathyroid hyperplasia | 90 | Thakker 2014[197]; Almeida and Stratakis 2010[199] |
| | Entero-pancreatic neuroendocrine tumor | 30-70 in patients; | |
| | Pituitary adenoma | 80 at autopsy | |
| MEN2/MEN2A | Medullary thyroid carcinoma (MTC) | 30-40 | |
| | PHEO | 90 | |
| | Parathyroid adenoma | 50 | |
| MEN2B | Medullary thyroid carcinoma | 20-30 | |
| | PHEO | >90 | |
| CDKN1B-related MEN | Parathyroid adenoma | 40-50 | Thakker 2014[197]; Lee and Pellegata 2013[200]; Marinoni and Pellegata 2011[201] |
| | Pituitary adenoma | 81 | |
| | Reproductive organ tumors | 41.6 | |
| | Adrenal and renal tumors | Insufficient data | |

**Table 4.3**

| Prevalence and incidence of PGL and PHEO in associated diseases, from literature reviews, worldwide. | | |
|---|---|---|
| DISEASES ASSOCIATED WITH PGL AND PHEO SYNDROMES | PHEO/PGL PENETRANCE | REFERENCES |
| MEN2A | 50 | Almeida and Stratakis. 2010[199]; Karasek et al. 2013[208] |
| MEN2B | 40–50 | Almeida and Stratakis. 2010[199] |
| SDHx-related PGL | Up to 70% | Kantorovich et al. 2010[209] |
| VHL | 1–20 | Almeida and Stratakis. 2010[199]; Karaskek et al. 2013[208]; Lefebvre and Foulkes. 2014[210]; Kirmani and Young. 2008[211] |
| NF1 | 0.1–5.7 | Almeida and Stratakis. 2010[199]; Lefebvre and Foulkes. 2014[202,210] |
| Carney-Stratakis syndrome or dyad | Very rare | Carney and Stratakis. 2009[212] |
| Carney triad | Very rare | Carney. 2009[213] |
| 3PAS | Very rare | Xekouki et al. 2015[214] |

Abbreviations: MEN, Medullary Endocrine Neoplasia; NF1, Neurofibromatosis type 1; PAS, pituitary adenoma with paraganglioma/pheochromocytoma.

In a database search1of 31 studies involving 5,031 patients (mean age 44 years) genetically tested for mutations in any of 11 genes (*NF1* and *RET*, *VHL*, *SDHD* and *SDHC*, *SDHB*, *SDHAF2*, *SDHC* and *TMEM127*, *MAX*, *IDH*), the frequency of germline mutations was 11-13%, and the most common of these mutations was *SDHB* (4.6%).[198] However, the true number of patients with apparently sporadic PHEO/PGL with an underlying germline mutation is likely even higher as the study also included patients with only partial genetic testing.

Sequencing showed that ~70% of skull base and neck PGL (HNPGL) cases carried mutations in the genes *SDHB*, *SDHC* and *SDHD*.[211] In a series of PGL and PHEO cases in France (n=202), 45.5% of the tumors had a germline or somatic mutation.[215]

In a retrospective review of 85 patients with MEN2-associated PHEO (81% Caucasian, 68% with family history of Medullary thyroid carcinoma (MTC), 67% family history of PHEO; in one cancer center (1960-2012, US), 82% had MEN2A and the remaining 18% had MEN2B. Five germline *RET* mutations were identified in 73% of patients, of which the most common were in codons 634 (69%) and 918 (8%). The most common MEN2-PHEO associated mutation (codon 634), was not associated with advanced stage MTC at diagnosis or a shorter survival.[218]

A study in 17 independent referral centers (in Europe and US) identified germline *MAX* mutations by DNA screening in 1.12% of PGL and/or PHEO patients with no other known mutations (genetic screenings n=1,694; frozen tumors n=245).[219]

The age at onset for sporadic cases is later in life at ~40-50 years compared to before 40 years in inherited PHEO cases. In a 2002 study of registries in Germany and Poland, of 271 non-syndromic (assumed sporadic) cases of PHEO (155 female, 116 male, age range 4-81 years, mean age 40 years) with no family history of the disease, 24% (n=66) of patients were identified as having a germline mutation in 1 of 4 genes screened (*VHL*, *RET*, *SDHD*, and *SDHB*). The mean age at onset at tumor presentation for sporadic cases was later in life than for hereditary disease (Table 4.4).[216] In later studies, the number was estimated to be even higher (~30%).

Several specific subtypes of *SDHx*-related hereditary PGL and related syndromes have been subclassified. Carney-Stratakis syndrome is a subcategory of *SDHx*-related, inherited tumor syndromes predominantly presenting with the dyad of PGL and gastrointestinal stromal tumor (GIST). The annual worldwide incidence of Carney-Stratakis (dyad) syndrome is <1 per million.[213] The syndrome was identified in fewer than 20 families, some with germline mutations in *SDHA*, *SDHD*, *SDHC* and *SDHB*.[211,212] The third condition is Carney triad, where tumors affect at least five organs, including stomach, lungs, the paraganglionic system, the adrenal system, and the oesophagus. The prevalence of tumors in Carney triad patients is outlined in Table 4.5. The hereditary basis of most Carney triad remains unknown, with the exception of a few cases that have been linked to *SDHx* (*SDHA*, *SDHB*, *SDHC*, *SDHD*) mutations.[220] All cases, however, share abnormal methylation of the SDHC promoter. Both subtypes can also be caused by somatic methylation of, for example, the *SDHC* locus.[221]

### 4.1.3 Carney complex

The annual worldwide incidence of Carney complex is <1 per million, of which ~70% of cases are inherited and due to a genetic variants in *PRKAR1A*.[222,223] The Carney complex is a rare, dominantly inherited syndrome associated with spotty skin pigmentation, myxomas, and endocrine overactivity. The most common endocrine tumor associated with Carney complex is primary pigmented nodular adrenocortical disease.[224] The prevalence of the most common clinical symptoms of Carney complex is presented in Table 4.6.

## 4.2 COST BURDEN OF DISEASE

Due to the rarity of all hereditary endocrine neoplasia syndromes, cost benefit and cost-effectiveness analyses are not available. In general, as evidenced in other hereditary diseases, such as Lynch syndrome, it is likely that there is a benefit in genetic testing and screening certainly with regards to morbidity and mortality and possibly with regards to cost-effectiveness.

**Table 4.4**

**Prevalence and incidence of PGL and PHEO in associated diseases, from literature reviews, worldwide.**

| DATA SOURCE | POPULATION | DISEASE PHENOTYPE | MUTATIONS | PROPORTION (%) | AGE AT PRESENTATION (YEARS) | NO. PATIENTS WITH AGE AT ONSET ≤18 YR |
|---|---|---|---|---|---|---|
| PHEO patients from population registries in Freiburg, Germany and Warsaw, Poland. | Total assumed sporadic cases (n=271); PHEO (n=241), PGL (n=22), PHEO+PGL (n=8); female (n=155), male (n=116), age range 4-80 years, mean age 40 years | Total (n=271) | | | 39.3 | 48 |
| | | Actual non-syndromic (sporadic) (n=205) | | 76 | 43.9 | 21 |
| | | Hereditary predisposition to VHL, MEN2, PHEO, PGL (n=66) | Deleterious germline mutations in *VHL, RET, SDHD, SDHB* | 24 | 24.9 | 27 |
| | | **Hereditary cases with germline mutations (n=66)** | | | | |
| | | Von Hippel-Lindau (n=30) | *VHL* | 45 | 18.3 | 20 |
| | | MEN2 (n=13) | *RET* | 20 | 36.4 | 0 |
| | | PHEO-PGL (n=11) | *SDHD* | 17 | 28.7 | 3 |
| | | PHEO-PGL (n=12) | *SDHB* | 18 | 25.6 | 4 |

Source: Neumann et al. 2002[216]

Abbreviations: PGL, paraganglioma; PHEO, pheochromocytoma; MEN2, multiple endocrine neoplasia.

**Table 4.5**

**Prevalence of tumors in Carney triad, worldwide.**

| DATA SOURCE | CLINICAL MANIFESTATION OF CARNEY TRIAD | PREVALENCE IN CARNEY TRIAD PATIENTS (%) |
|---|---|---|
| Among 77 patients with Carney triad, Worldwide | Gastric stromal tumor | 75 |
| | Pulmonary chondroma | 15 |
| | Extra-adrenal PGL | 10 |
| | Adrenocortical adenoma | 20 |
| | Esophageal leiomyoma | 10 |

Source: Carney. 2009[213]

4.3

## DEMOGRAPHIC DIFFERENCES

In general, it is important to note that although gender differences exist with regards to associated tumor risks, most studies are small and may be influenced by small sample sizes and ascertainment bias.

4.3.1

### Multiple Endocrine Neoplasias

In 2011, Goudet and colleagues in France reported that females diagnosed with MEN1 had a greater probability of developing pituitary tumors, and males had a greater probability of developing the ZES/gastrinomas type of duodeno-pancreatic tumors. While no sex differences were identified in other duodeno-pancreatic tumors, thymic tumors were found exclusively in males (Table 4.7). A family history of MEN1 was found more frequently in males at the time of diagnosis.[226]

4.3.2

### SDHB-related PHEO and PGL

A 2017 report of 241 mutation carriers (asymptomatic relatives of patients) showed 16.6% (n=40) developed PHEO/PGL during the study with a penetrance of 49.8% at 85 years. Males had a higher age-related penetrance of disease with 50% penetrance at 74 years vs. not reached. There was no association between mutation and gender or tumor location.[227]

4.3.3

### Carney complex

The female to male ratio of Carney complex is 2.4:1.[224] Carney triad is by far more likely to be seen in females (85%) than males (15%).[213]

**Table 4.6**

Prevalence of clinical symptoms associated with Carney complex from literature reviews, worldwide.

| CLINICAL SYMPTOMS OF CARNEY COMPLEX | PREVALENCE IN CARNEY COMPLEX (%) | REFERENCES |
|---|---|---|
| Spotty skin pigmentation | >80 | Almeida and Stratakis. 2010[224] |
| Cardiac myxomas | 30-60 | Almeida and Stratakis. 2010[224]; Bertherat. 2006[222] |
| Primary pigmented nodular adrenocortical disease (PPNAD) | 25-60 | |
| Testicular tumors | 33-56 | Bertherat. 2006[222] |
| Growth-hormone producing pituitary adenoma | 12 | Almeida and Stratakis. 2010[224] |
| Thyroid tumors/cancer | 10-25/2.5 | Almeida and Stratakis. 2010[224]; Bertherat. 2006[222] |
| Psammomatous melanotic scwannoma | 8-18 | |
| Pancreatic cancer | 2.5 | Gaujoux et al. 2011[225] |

**Table 4.7**

Significant differences in the prevalence of MEN1 characteristics by sex.

| | | | | PREVALENCE (%) | |
|---|---|---|---|---|---|
| DATA SOURCE | STUDY | POPULATION | DISEASE CHARACTERISTICS OF MEN1 | FEMALES | MALES |
| Multicenter 'Groupe d'etude des Tumeurs Endocrines', 22 regions, 1956-1991 | Cohort study | France and Belgium, MEN1 (57.8% female) (n=734) | Pituitary tumors | 46.5 | 30.3 |
| | | | Pituitary tumors: patients diagnosed with MEN1 at time of 1st lesion | 44.2 | 67.3 |
| | | | Thymic tumors | 0 | 6.1 |
| | | | Duodeno-pancreatic: ZES/gastrinomas | 24.3 | 36.5 |
| | | | Pituitary tumors (patients diagnosed with MEN1 at time of 1st lesion); n=55 | 44.2 | 67.3 |

Source: Goudet et al. 2011[226]

## 4.4 LIFE EXPECTANCY AND MORTALITY

### 4.4.1 Multiple endocrine neoplasias

The care of patients with MEN1 can be challenging, often requiring a multidisciplinary team of healthcare workers.[197,199] Studies indicate that between 28% and 70% of deaths in MEN1 patients are a direct result of MEN1, often due to malignant pancreatic neuroendocrine tumors (pNETs), gastrinomas, and foregut carcinoids.[197] Improved knowledge, early diagnosis due to screening for genetic mutations, as well as routine surveillance and biochemical testing and imaging in asymptomatic relatives, has improved patient outcome in MEN syndromes.[228]

In 85 MEN2 patients with PHEO (retrospective review between 1960-2012 at one cancer center in the US), there had been deaths in 24% of cases (median age at death 38 years), which had been mostly linked to PHEO (10%), or MTC (85%). Of 107 patients with the most common mutation (codon 634), all had MTC and 55% had PHEO. Of the patients with PHEO, survival after MEN2 diagnosis was 100% at 5 years, 98% at 10 years, and 90% at 15 years. For patients without PHEO, the survival rates were lower, at 98%, 85%, and 78%, respectively. The median survival times were 499 months with PHEO, and 444 months with MTC only. Each year of delay in MTC diagnosis increased the chance of death by 6%, and each 1-cm increase in PHEO size at time of diagnosis was associated with an HR for death by 1.5. MTC-patients without PHEO had three-times higher risk-of-death than patients with PHEO.[218]

In MEN2B, medullary thyroid carcinoma is often early onset. Prior to the availability of early diagnosis, patients did not survive beyond age 21 years, but with early diagnosis and thyroidectomy by age 1 year, patients can live a more normal life span.[229,230]

### 4.4.2 Hereditary Pheochromocytoma and paraganglioma syndromes

Germline mutations in the *SDHB* gene are likely to be associated with a higher morbidity and mortality than mutations in other *SDH* genes. Furthermore, PGLs associated with the *SDHB* mutation have a higher risk of becoming malignant (34-71%), than those associated with *SDHD* (<5%) or *SDHC* (low risk) germline mutations.[211]

In a 2014 retrospective US study of 106 PHEO/PGL patients with *SDHB* mutations, there were no significant differences in survival based on specific *SDHB* mutations or patient sex. However, the study found metastatic disease developed significantly earlier in patients with larger (≥4.5cm) tumors, and those with primary tumors larger than 5.5cm had significantly worse overall survival than those with smaller tumors. In PGL, the size of the tumor was an age-independent predictor of patient survival and metastases development, and in both PHEO and PGL, age at diagnosis was found to be an independent predictor of patient survival.[231]

Approximately 10-20% of PGLs/PHEOs are metastatic. A higher potential for metastasis was observed in succinate dehydrogenase subunit B/fumarate hydratase (*SDHB*/*FH*)-associated tumors, and the age of onset of primary tumors was earlier for those with *SDHB* mutations (Table 4.8).

Mutations in *SDHB* are linked to more aggressive tumors, with a higher metastatic rate (34-71%) than other PGLs/PHEOs (Table 4.9).[231] The overall 5-year survival of PGL or PHEO patients with SDHB mutations was 75.7%. The 5-year survival probability from initial diagnosis for

**Table 4.8**

**Metastatic PGL/PHEO diagnosed and treated between 2000 to 2014, US.**

| | | | TUMOR TYPE | |
|---|---|---|---|---|
| DATA SOURCE | STUDY | POPULATION | SDHB MUTATIONS | APPARENTLY SPORADIC TUMORS (AST) |
| Retrospective study at the National Institute of Health (NIH, 2000-2014 | US (n=132); children (n=27), adults (n=105); 58% males, 42% females | Prevalence (%) | 55 | 45 |
| | | Age at primary tumor (years) | 31 ± 16 | 40 ± 15 |
| | | Metastatic tumors at 1st diagnosis (%) | 23+ | 15 |

Source: Turkova et al. 2016[232]

patients with or without synchronous metastasis was 74.5% and 96.4% respectively. The authors also reported that an increase in tumor size predicted a decrease in survival, and an increase in metastasis. For tumor sizes ≤4cm, 4-6cm, 6-9cm, and >9cm, the probability of 5-year survival was 94.1%, 95%, 83.4% and 88% respectively, and the median years to death were >55, >25, 12, and 20, and the survival HR was 1.0, 4.6, 12.2 and 5.8 respectively for PGL/PHEO cases.[231]

The phenotypes, malignancy rates, and survival rates of genes linked to familial PGL/PHEO are outlined in Table 4.10.

In an international study, *SDHC* mutations were reported in 4% of head and neck PGL (HNPGL) cases and were absent in PHEO index cases (Table 4.11). The authors also reported that patients with *SDHC* mutations had a younger age at diagnosis than patients with sporadic PGL (45 and 52 years, respectively).[236]

The rate of metastatic disease in children with PHEO/PGL has been described to be between 9% and 47%, and up to 70% in children age <10 years. In a study of 263 cases of PHEO/PGL (2000-2010), metastatic disease was described in 125 (47.5%) of cases. Of these patients, 49 (39%) presented with a tumor before age 20 years, and 32 (65%) of these 49 cases had metastatic disease, with the latter showing a high prevalence of *SDHB* germline mutations (Table 4.12).[204]

The 5-, 10- and 20-year survival rates for the children (n=49) were 97.6%, 97.6%, and 83.7% respectively.[204]

In a recent retrospective US study of PGL/PHEO cases (n=106) associated with *SDHB* mutations, the 5-year survival rates for primary tumors were 94.1% for ≤4cm, 83.4% for 6-9cm, and 88% for >9cm. Of the patients that developed metastatic disease (72.6%), for tumors ≥5.5cm, the 5-year survival rates with or without metastatic disease were 65.8% and 97.1%.[231]

In a 2008 study from Belgium of 56 cases of PHEO and/or PGL (Table 4.13), mutations were identified in 41% of cases. Of the 23 familial cases, 19 were of HNPGL and 4 were abdominal PHEO/PGL.[203] Surprisingly, the normally malignant *SDHB* mutations in sympathetic PGL showed unilateral, late onset symptoms, and no evidence of recurrence or malignancy. In 2012, the authors provided an update of 59 HNPGL, and 53 PHEO cases (between May 2003 to May 2011). The prevalence of mutations in *SDHx* genes was 44% in all HNPGLs, and 37% in apparently sporadic cases. In the latter group, *SDHB* and *SDHD* mutations were detected in 20% and 18% of cases respectively.[237]

### 4.4.3
### Carney complex

Most individuals with Carney complex have a normal lifespan, but some die at an early age, resulting in an estimated average life expectancy of 50 years.[223] However, this estimate is based on historic data, and regular screening and improvement in care is expected to reduce associated morbidity and mortality.

Carney triad is chronic, persistent and frequently indolent.199 In a US study of 104 cases, patients commonly presented with gastric bleeding, 47% showed metastasis, and 13% died of metastatic GIST at a mean age of 45 years. The 40-year survival was 73%, and the 10-year survival was 100%.[238]

## 4.5
## KEY TRENDS AND HEALTH OUTCOMES

A 2016 retrospective review of 291 MEN1 patients at a tertiary referral centre (1980-2014), reported a 10-year

**Table 4.9**

**Differences in tumor size and survival probability in SDHB-associated PGL and PHEO, US.**

| STUDY | POPULATION | MEASUREMENT | PGL | PHEO |
|---|---|---|---|---|
| Retrospective study, National Institute of Health referral center | US, n=106 PHEO/PGL patients with SDHB mutations; n=39 females, n=67 males; metastatic disease in n=106 (72.6%) | Number of patients (n) | 89 | 17 |
| | | Median age at initial diagnosis (years) | 29 | 31 |
| | | Median sizes of primary tumors (cm) | 6 | 8 |
| | | 5-year survival probability without synchronous metastasis (%) | 97.9 | 88.9 |
| | | 5-year survival probability with synchronous metastasis (%) | 73.2 | 80.0 |

Source: Schovanek et al. 2014[231]

**Table 4.10**

| Phenotype associated with gene mutations for PGL/PHEO from literature reviews, worldwide. | | | | | |
|---|---|---|---|---|---|
| GENETIC MUTATION | PHENOTYPE | MEAN AGE AT DIAGNOSIS (YEARS) | MALIGNANCY RATE (%) | 5-YEAR SURVIVAL RATE (%) | REFERENCE |
| Sporadic | PGL/ PHEO | 40-50 | N/A | N/A | Lefevbre and Foulkes. 2014[210] |
| *RET* | PHEO | 30-40 | 1–5 | N/A | Karasek et al. 2013[208] |
| *VHL* | PHEO and rarely PGLs | 30 | <5 | N/A | |
| *NF1* | PHEO and rarely extra-adrenal PGLs | 40-42 | 0-12 | N/A | Lefevbre and Foulkes. 2014[210]; Karasek et al. 2013[208] |
| *SDHAF2* | PGL | 30-40 | rare | N/A | Lefevbre and Foulkes. 2014[210]; Karasek et al. 2013[208]; Kantorovich et al. 2010[233]; Kirmani and Young. 2008[211] |
| *SDHA* | PGL | N/A | 0-14 | N/A | Kirmani and Young. 2008[211]; Karasek et al. 2013[208] |
| *SDHB* | PGL and PHEO | 25-30 | 34-71 | 36 | Almeida and Stratakis. 2010[199]; Kantorovich et al. 2010[233]; Chetty. 2010[234]; Karasek et al. 2013[208]; Lefebvre and Foulkes. 2014[210] |
| *SDHC* | PGL | 35-38 | Rarely | N/A | Almeida and Stratakis. 2010[199]; Kantorovich et al. 2010[233]; Chetty. 2010[234]; Else et al. 2014[122]; Karasek et al. 2013[208]; Lefebvre and Foulkes. 2014[210]; Kirmani and Young. 2008[211] |
| *SDHD* | PGL, PHEO | 40-50 | <5 | N/A | Alameida and Stratakis. 2010[199]; Kantorovich et al. 2010[233]; Chetty. 2010[234]; Lefebvre and Foulkes. 2014[210]; Kirmani and Young. 2008[211]; |
| *MAX* | Predisposed to PHEO; possibly PGL | 32 | 25 | N/A | Kirmani and Young. 2008[211]; Karasek et al. 2013[208] |
| *TMEM127* | PHEO only | 42-45 | <5 | N/A | Kirmani and Young. 2008[211]; Qin et al. 2010[235]; Karasek et al. 2013[208]; Lefebvre and Foukes. 2014[210] |

Abbreviations: N/A, not available.

**Table 4.11**

| Tumors associated with mutations in SHD gene family in PHEO syndrome, worldwide. | | | | | |
|---|---|---|---|---|---|
| DATA SOURCE | POPULATION | | PERCENTAGE OF PATIENTS WITH CARTOID BODY TUMORS (%) | PERCENTAGE OF PATIENTS WITH MULTIPLE TUMORS (%) | PERCENTAGE OF PATIENTS WITH MALIGNANT TUMORS |
| PHEO registry, Jan 2001-Dec 2004 | Unrelated index cases (n=121), sporadic cases (n=371) | SDHC (n=22) | 59 | 9 | 0 |
| | | Sporadic HNP (n=90) | 32 | | |
| | | SDHB (n=15) | | | 40 |
| | | SDHD (n=42) | | 57 | |
| Source: Schiavi et al. 2005[236] | | | | | |

**Table 4.12**

**Tumors associated with mutations in SHD gene family in PHEO syndrome, worldwide.**

| DATA SOURCE | POPULATION | MUTATION | PREVALENCE (%) TUMOR AGE <20 YRS METASTATIC N=32 | PREVALENCE (%) TUMOR AGE <20 YRS NON-METASTATIC N=17 |
|---|---|---|---|---|
| National Institutes of Health, 2000-2010 | PGL/ PHEO (n=263), metastatic disease (n=32) age <20 years, non-metastatic disease (age <20 years) | *SDHB* | 71.9 | 23.5 |
| | | *SDHD* | 9.4 | 5.9 |
| | | *VHL* | 6.3 | 23.5 |
| | | *NF1* | 0 | 11.8 |
| | | No mutation (sporadic) | 12.5 | 35.3 |

Source: King et al. 2011[204]

**Table 4.13**

**Prevalence of *SDHD* and *SDHB* mutations in head and neck PGL, Belgium.**

| DATA SOURCE | POPULATION | DISEASE TYPE | MUTATION | PREVALENCE (%) |
|---|---|---|---|---|
| Cliniques Universitaires Saint Luc, May 2003 - May 2006 | Belgium, PHEO and/or PGL patients (n=56), head and neck PGL (familial n=6, sporadic n=30), abdominal PHEO/PGL (n=18), PGL of the cauda equine (n=2) | *Familial head & neck PGL cases* | *SDHD* | 100 |
| | | *Sporadic cases* | *SDHD* | 13 |
| | | | *SDHB* | 27 |

Source: Persu et al. 2008[203]

overall survival rate of 45% and a 10-year disease-free survival rate of 42%.[239] In 2014, Dy and colleagues reported that for 30 MEN1 patients who underwent resection for neuroendocrine tumors at a single tertiary care center (1994-2010), the estimated 10-year survival was 86.4%, and the disease-free interval was 89% for 1 year, 50% for 5 years, and 19% for 10 years.[240]

Approximately 20% of sporadic PGL/PHEO cases carry somatic mutations in NF1 and approximately 10% of these are metastatic.[241] In metastatic PHEO/PGL, the 5- and 10-year survival rates were significantly better in patients with apparently sporadic tumors (AST) than those with *SDHB* mutations (p value 0.01). In individuals with *SDHB* mutations, children had significantly longer survival than adults.[232]

Inherited, bilateral PHEO tumors can be treated by open total bilateral adrenalectomy, although patients may suffer from permanent adrenal insufficiency, requiring lifelong steroid replacement. Cortex-sparing adrenalectomy is the preferred option although it presents a higher chance of recurrence.[242]

Patients with *SDHB* mutations have a higher response rate to targeted therapy with 123I-metaiodobenzylguanidine (MIBG). In malignant PGL and PHEO patients treated with MIGB, the tumor response rate ranged from 22 to 48%. Of those responding to MIBG treatment, between 35 and 67% exhibited a biochemical response.[241] Targeted radiotherapy with 90Y-DOTATOC and 177Lu-DOTATOC results in <10% response rates, but overall has not been well explored. Malignant tumors associated with *SDHB* mutations are often deficient in O6-methylguanine-DNA methyltransferase (MGMT), and so respond better to cyclophosphamide-vincristine-decarbazine (CVD) regimen or to the less toxic temozolomide (TMZ) therapy than non- *SDHB* such as sporadic cases.[241] In one study (n=18), a complete/partial response was detected in 55% of patients. A modified CVD regimen with doxorubicin in malignant PGL/PHEO patients (n=13) showed a 46% partial response rate. TMZ therapy resulted in response rates that were partial (33%), stable (47%), and progressive (20%) in 15 malignant PGL/PHEO cases where 67% of patients (n=10) carried an *SDHB* mutation.[243]

Between May 2008 and January 2013 in Greece, 17 patients (11 sporadic, 6 MEN2A-associated PHEO) with a

mean tumor size of 3.7cm had undergone retroperitoneal adrenalectomy (PRA) and 17 patients (13 sporadic PHEO, 4 MEN2A syndrome) with a mean tumor size of 5.1cm had undergone the laparoscopic technique. There was no mortality and no blood transfusions were needed for either group. PRA proved to have better clinical results than laparoscopic techniques for sporadic and inherited PHEO: mean hospital stay was 2.1 days for PRA and 4 days for the laparoscopic group; mean operative times were 105.6 and 137 minutes respectively.[244]

The treatment and outcome of a number of endocrine cancers are shown in Table 4.14. Subtotal parathyroidectomy is the initial treatment of choice for primary hyperparathyroidism in MEN1 patients, while total parathyroidectomy with autotransplantation may be used in cases of extensive disease at initial or repeat surgery.[245]

# V PARATHYROID CARCINOMAS

## 5.1 PREVALENCE AND INCIDENCE

Parathyroid carcinomas are indolent neoplasms, and one of the least common endocrine tumors, occurring with an incidence of 0.015 per 100,000 of the population.[254] While the majority of cases arise sporadically, risk factors include a history of head and neck irradiation, familial isolated primary hyperparathyroidism, multiple endocrine neuroplasia type 1, and hereditary hyperparathyroidism-jaw tumor (HPT-JT) syndrome (*CDC73*-related disorder).

The clinical presentation of parathyroid carcinomas in syndromic patients is similar to non-syndromic patients.[255] The prevalence of parathyroid carcinomas in patients with primary hyperparathyroidism is normally <1% worldwide, although a 5% occurrence is reported in cases of primary hyperparathyroidism in Italy and Japan (Table 5.1). The highest prevalence of parathyroid carcinoma is in HPT-JT syndrome (Table 5.1), an autosomal dominant disease characterized by parathyroid and fibroosseous tumors of the jaw bone.[256] However, the vast risk increase might be due to an initial ascertainment bias due to recruitment and analysis of patient with specifically parathyroid cancer.

A US study of 286 cases of parathyroid carcinomas from the National Cancer Data Base (NCDB) over a 10-year period (1985-1995) revealed neither tumor size nor lymph node status were prognostic factors for parathyroid carcinomas.[257]

The age at diagnosis of parathyroid carcinomas can vary from 19 to 81 years, with a median age normally between 30 and 40 years.[258]

## 5.2 COST BURDEN OF DISEASE

The disease is too rare to determine.

## 5.3 DEMOGRAPHIC DIFFERENCES

The female-to-male ratio is reported to be 3-4:1 for primary hyperparathyroidism and 1:1 for parathyroid carcinoma.[254,259] No differences were observed in age or ethnicity, except for possible parathyroid carcinoma clustering by country/region, as mentioned above (Table 5.1).[256]

## 5.4 LIFE EXPECTANCY AND MORTALITY

Parathyroid carcinomas are described as indolent and tenacious, with a low potential for malignancy.[254] Mortality in patients with functioning parathyroid carcinomas is usually a result of metabolic complications due to hypercalcemia (eg. renal failure, cardiac arrhythmia, or pancreatitis), rather than the tumor itself, whereas mortality in cases of non-functioning parathyroid carcinoma often arises from tumor burden.[256,260,261] In 2011, Harari and colleagues published a retrospective 43-year analysis of 37 parathyroid carcinoma patients in the US. After diagnosis, 60% of patients developed complications due to treatment: unilateral or bilateral vocal cord paralysis was reported in 38% of patients; temporary and permanent hypocalcemia was identified in 21.6% and 5.4% of patients, respectively; and lymph node and distant metastases were reported in 30% of cases (with a mean time to distant metastasis of 6.3 years). Recurrences were seen in 49%, with a time to first recurrence between 1.2 to 92 months (mean 29.9 months), and the overall median survival was 14.3 years.[261] The most notable predictors of recurrence were lymph node metastasis (HR, 4.27) or distant metastasis (HR, 3.5) when compared to no metastasis.

In 2013, Allen and colleagues reported that performing the intact parathyroid hormone assay did not improve the overall survival in parathyroid carcinoma (comparing cases before and after the introduction of the assay: 1973-1997 vs. 1997-2006) (Table 5.2). However, older age (≥56 years), black race, and an unknown extent of disease, all increased the risk of mortality from any cause.[262] Similarly,

**Table 4.14**

**Outcomes of treatments for familial endocrine cancers.**

| ENDOCRINE CANCER | TREATMENT | OUTCOME | REFERENCES |
|---|---|---|---|
| | | **Parathyroid tumors** | |
| MEN1 | Subtotal parathyroidectomy (removal of ≤3.5 glands) | 40-60% of patients had persistent or recurrent hypercalcemia within 10-12 years post surgery | Thakker et al. 2012[245]; Giusti et al. 2005 |
| | | 10-30% of patients had hypocalcemia requiring long-term therapy with Vitamin D or calcitriol. | |
| | Total parathyroidectomy with autotranplantation | >50% of patients had recurrent hypercalcemia | |
| MEN2A | Preventative thyroidectomies in 50 patients in group A involving central neck dissection with total parathroidectomy and autotransplantation of parathyroid slivers to forearm or neck (1993-2000); compared to group B of 97 MEN2A (5 MEN2B) patients with preventative thyroidectomies, preserving parathyroid glands (2003-2015). | Permanent hypoparathyroidism occurred in 6% of group A and 1% of group B. After total thyroidectomy, no patient in either group developed permanent recurrent laryngeal nerve injury or hyperparathyroidism. | Moley et al. 2015[246] |
| | | **Well-differentiated tumors of the gastro-entero-pancreatic (GEP) tract** | |
| a) Gastrin-secreting tumors gastrinomas (60-80% of cases) | | | |
| *MEN1* | Surgery recommended for tumors at pancreatic islet, stomach endocrine cells, or duodenum. Medications can be used to control some of the gastro-entero-pancreatic hormone excess. | Surgery: 77% cure rate by pancreatoduodenectomy in 12 MEN1-associated hypergastrinomas. | Tonelli et al. 2005[247] |
| | Surgery | 15% of MEN1 patients were free of disease immediately after surgery; 5% were free of disease 5 years after surgery. | Thakker et al. 2012[245] |
| | Long-term administration of Somatostatin analogues: octreotide, and lanreotide | Type II gastric carcinoid tumors in patients with combined MEN 1 and the Zollinger-Ellison syndrome, 2 patients treated with lanreotide (30mg every 10 days) and 1 patient with octreotide (20mg every 28 days) with follow up at 6 months and 1 year. Tumor regression (with reduction in size and number) in all 3 patients after 6 months and complete disappearance after 1 year of treatment. | Waguespack et al. 2010[248]; Tomassetti et al. 2000[249] |
| | Gastric carcinoid tumors in Zollinger-Ellison syndrome (ZES) patients (n=231); and in patients with both ZES and MEN1 (n=45). Proton-pump inhibitors (eg. omeprazole or lasoprazole) to treat gastric acid hypersecretion; some may also require histamine H2 receptor antagonists (cimetidine or ranitidine). Gastric carcinoid tumors in 13-30% ZES with MEN1 and ZES and 0-0.6% in ZES without MEN1. | Acid secretion controlled with Omeprazole (65mg/day) for up to 14 years (mean 6.2 years); with Ranitidine, (2700mg/day) for up to 15 years (mean 5.9 years). Once acid secretion is controlled, patients with MEN1 have better long-term survival than those without MEN1. | Jensen. 1998[250] |

| Outcomes of treatments for familial endocrine cancers. (continued) | | | |
|---|---|---|---|
| ENDOCRINE CANCER | TREATMENT | OUTCOME | REFERENCES |
| **Insulinomas (20% of cases)** | | | |
| Pancreatic neuroendocrine tumors | Adrenalectomy in 96 patients (47 with bilateral disease). Originally unilateral adrenalectomy was performed in 30% of patients, and PHEO developed in contralateral gland after 1-20 years post diagnosis (median 8.2 years) | Cortical-sparing adrenalectomy avoided long-term corticosteroid dependence in most cases. 7% (4/55) recurrences in cortical-sparring remnants, 3% (3/101) recurrences in adrenal bed after total adrenal resections. Acute adrenal insufficiency developed in 20% (5/25) of patients who underwent total bilateral adrenalectomy. Acute adrenal insufficiency developed in 3% (1/39) who underwent cortical-sparring adrenalectomy. Of these with adequate follow-up, 78% (21/27) were steroid independent at 3-year follow-up. | Kazanjian et al. 2006[251] |
| **Hereditary PHEO** | | | |
| Hereditary PHEO | Adrenalectomy in 96 patients (47 with bilateral disease). Originally unilateral adrenalectomy was performed in 30% of patients, and PHEO developed in contralateral gland after 1-20 years post diagnosis (median 8.2 years) | Cortical-sparing adrenalectomy avoided long-term corticosteroid dependence in most cases. 7% (4/55) recurrences in cortical-sparring remnants, 3% (3/101) recurrences in adrenal bed after total adrenal resections. Acute adrenal insufficiency developed in 20% (5/25) of patients who underwent total bilateral adrenalectomy. Acute adrenal insufficiency developed in 3% (1/39) who underwent cortical-sparring adrenalectomy. Of these with adequate follow-up, 78% (21/27) were steroid independent at 3-year follow-up. | Grubbs et al. 2013[252] |
| **Carney complex** | | | |
| Cardiac myxomas | Surgery of myxomas of the heart | 35% recurrence, most diagnosed in first 4 years post surgery. Recurrence risk: 12-22% for familial and 1-3% for sporadic tumors. | Reynen. 1995[253] |

Abbreviations: PGL, Paraganglioma; PHEO, Pheochromocytoma.

**Table 5.1**

| Prevalence and Incidence of parathyroid carcinomas, from literature reviews, worldwide. | | | |
|---|---|---|---|
| POPULATION | PREVALENCE (%) | INCIDENCE (PER 100,000) | REFERENCES |
| US, all reported cancer cases in the National Cancer Database, 1985-1995 | 0.005 | N/A | NCI. 2013[254]; Kassahun and Jonas. 2011[256] |
| Primary hyperparathyroidism | | 0.015, US | NCI. 2013[254]; Hsu et al. 2014[259] |
| Worldwide, primary hyperparathyroidism | 0.17–5.2 | N/A | NCI. 2013[254]; Kassahun and Jonas. 2011[256] |
| US, multiple endocrine neoplasia 1 (MEN1) patients (n=348, 54.5% females, mean age at diagnosis 48.3 years) | 0.28 | N/A | Ospina et al. 2015[255] |
| Worldwide, hyperparathyroidism-jaw tumor (HPT-JT) syndrome | Up to 15 | N/A | Kassahun and Jonas. 2011[256] |

Abbreviations: N/A, not available, NCI, National Cancer Institute.

**Table 5.2**

**Survival data for patients with parathyroid carcinoma.**

| DATA SOURCE | POPULATION | 5-YEAR MEDIAN SURVIVAL (YEARS) | 5-YEAR OVERALL SURVIVAL (%) | 10-YEAR OVERALL SURVIVAL (%) | 5-YEAR DISEASE-SPECIFIC SURVIVAL (%) | REFERENCES |
|---|---|---|---|---|---|---|
| SEER database 1973-1997 | n=142 | 15.6 | 78 | 61.2 | 88 | Allen et al. 2013[262] |
| SEER database 1997-2006 | n=228 | | 82 | N/A | 96 | |
| SEER Database 1988-2003 | n=224 | N/A | 83.9 | 67.8 | 91 | Lee et al. 2007[264] |
| National Cancer Data Base, 1998-2011; ≥60 month follow-up | n=528 | N/A | 81.1 | N/A | N/A | Sadler et al. 2014[263] |
| Literature review | N/A | N/A | 40–86 | 49–77 | N/A | Kassahun and Jonas. 2011[256] |
| National Cancer Data Base, 1985-1995 | n=286 | N/A | 85.5 | 49.1 | N/A | Hundahl et al. 1999[257] |
| The Netherlands | n= 41 | N/A | N/A | 71 | 79 | Schaapveld et al. 2011[265] |
| SEER database 1988-2010 | n=385 | N/A | 82.5 | 65.4 | 89.9 | Hsu et al. 2014[259] |

Abbreviations: N/A, not available.

from patient data in the National Cancer Data Base, in 2014, Sadler and colleagues reported that the mean overall survival was lower, and relative risk of death higher in older patients and in black patients with a secondary malignancy and ≥2 comorbidities. Positive lymph nodes (HR, 6.47) and older age (HR, 2.35) were associated with a lower overall survival after multi-variant cox regression.[263] In their 2007 US study, Lee and colleagues reported that the time to death was worse in males (HR, 2.37) and those with distant metastases (HR, 11.62), and also influenced by age at diagnosis (HR, 2.23) and year of diagnosis (HR, 0.9).[264] Furthermore, the authors reported that tumor size (HR, 1.18 for ≥4cm vs. HR, 1.0 for 0-1.9cm), lymph node status (HR, 2.84 for positive status) and type of surgery (HR, 0.55 for en bloc resection vs. 1.0 for all other surgeries; HR, 2.4 for radiation therapy) did not significantly impact overall survival rate.[264]

Parathyroid carcinomas have a tendency to be localized, invading tissues such as the thyroid gland, trachea, recurrent laryngeal nerve, or esophagus.[254] Metastases to regional lymph nodes and to distant sites are rare, and identified in <5% and <2% of patients, respectively.[254] In a 1999 US study of 286 cases from the National Cancer Database, 5.6% of parathyroid carcinoma patients showed lymph node metastasis.[257]

Lymph node examination in 114 cases of parathyroid carcinomas in the US SEER registry (1988-2010) revealed that 10.5% of tumors were lymph node positive. Tumors ≥3cm, were more likely than those <3cm, to show lymph node metastasis (21% vs. 2.8%). While positive lymph nodes did not appear to significantly impact disease-specific survival, tumor size ≥3cm (HR 5.35%) and distant metastases (HR, 45.1%) did negatively impact survival. As lymph node status is not significantly associated with metastases, lymphadenectomy has no proven benefit.[256,259] The overall disease-specific survival rates in the SEERs database were 95.1% for 5 years, and 89.9% for 10 years.[259] Despite the high overall survival rate in parathyroid carcinomas, the recurrence rate post surgery (from several studies) is also high (40-60%).[264]

5.5

## KEY TRENDS AND HEALTH OUTCOMES

A number of studies have reported a temporal increase in parathyroid carcinoma, including a 2007 study by Lee and colleagues who reported a 60% increase in incidence over a 16-year period in the US (Table 5.3).[264,266]

In a 2011 retrospective study, Brown and colleagues investigating all 21 confirmed cases of parathyroid carcinoma identified between 1958 and 2010 from the University of Sydney Endocrine Surgical Unit database, revealed that only 3 cases were reported in the first 30 years of the 52-year time span, while the majority (n=11) were identified in the last 5 years. No differences were identified in demographics or disease in presentation. The authors could not determine whether the observed increase in cases from 2006 to 2010 was a result of improved screening and diagnostics or a genuine increase in incidence.[266]

Treatment options and outcomes for parathyroid carcinomas are outlined in Table 5.4. Surgical resection is the recommended treatment for parathyroid carcinomas, with repeated resection for local and distant recurrences.[256] A 2011 literature review stated that ~80% of parathyroid carcinoma patients undergo simple parathyroidectomy while en bloc resection is performed on the remaining ~12%. These surgeries are not curative, and recurrence rates can be as high as 80%, and 10-year survival rates can be 50% or lower, with significant differences in the recurrence rates for these 2 procedures (Table 5.4).[256] Postsurgery, recurrence is observed in 40-60% of patients within 2-5 years, and is often preceded by hypercalcemia. Recurrence is usually in the neck or cervical lymph nodes in two-thirds of cases, and difficult to detect because of its multifocal nature and small size.[254] Control of hypercalcemia by reducing calcium in the blood is a significant issue in the treatment of parathyroid carcinomas. Bisphosphonates (clodronate, etidronate, and pamidrone) can inhibit bone resorption, calcimimetics such as cinacalcet can inhibit parathyroid hormone production, calcitonin is an only transiently effective anti-hypercalcemic agent, and monoclonal antibody denosumab can be an effective treatment to decrease calcium release from bone by inhibition of RANK ligand.[267-269] These treatments can be used in the short-term until surgery can be performed. Additional treatments on the horizon include dendritic cell immunotherapy and immunization with parathyroid hormone peptides.[256,270]

In functioning parathyroid carcinomas, recurrence can be as high as 100% within 1 to 6 years after parathyroidectomy. In non-functional parathyroid carcinomas, enbloc resection patients often succumb to systemic tumor burden with recurrence within 2 years.[256] En bloc resection (microscopically negative margins) shows 50% cure rate and 50% recurrence rate within 1-20 years (mean 3 years). The 5-year survival rate is 40-86%, and the 10-year overall survival rate is 49% (max. reported 77%).[256,260,271] While parathyroid carcinomas are thought to be resistant to radiation therapy, the latter is ineffective in decreasing hormone production and controlling tumor growth. Some single institution reports indicate a reduction in recurrence with post-surgery radiotherapy (Table 5.4); therefore, radiotherapy use is assessed on a case-to-case basis.[256,260,272]

In 2007, Lee and colleagues reported on parathyroid carcinoma treatments over a 16-year period (1988-2003) (Table 5.5). Although they noted no significant change in the use of radiation therapy from 8.3% in 1988-1991 to 10% in 2000-2003; there was a significant increase in the use of simple parathyroidectomies, from 70.8% to 84.2%, while patients undergoing no surgery decreased from 4.25 to 0.8%. Although en bloc resection was noted to decrease from 20.8% to 12.5%, this was not statistically significant.[264]

**Table 5.3**

Survival data for patients with parathyroid carcinoma.

| DATA SOURCE | POPULATION | TIME FRAME | INCIDENCE PER 100,000 |
|---|---|---|---|
| SEER database, 1988-2003 | US, parathyroid carcinoma (n=224) | 1988-1991 | 0.0358 |
| | | 1992-1995 | 0.0311 |
| | | 1996-1999 | 0.0457 |
| | | 2000-2003 | 0.0573 |

Source: Lee et al. 2007[264]

**Table 5.4**

| Treatment options and outcomes for parathyroid carcinoma. | | | | |
|---|---|---|---|---|
| CONDITION | POPULATION | TREATMENT | OUTCOME | REFERENCE |
| Non-functioning parathyroid carcinomas | Literature review of case reports, n=19; age 27-71 years at presentation, 1929-2009 | Initial surgical resection in 18/19 patients | ≥50% recurrence and 84% alive at time of case report (4-98 months); only 15.7% (n=3) have data >3 years. | Wilkins and Lewis. 2009[273] |
| Functioning parathyroid carcinomas | Literature review of 156 publications, 1993-1999, n=358, follow up in n=301, age 12-80 years (avg. 48 years at presentation), | En block resection of carcinoma and adjacent structures in the neck (n=104) | 8% recurrence rate, 89% long-term survival rate (follow up: mean 69 months). | Koea et al. 1999[274] |
| Functioning parathyroid carcinomas | Literature review of 156 publications, 1993-1999, n=358, follow up in n=301, age 12-80 years (avg. 48 years at presentation) | Simple parathyroidectomy (n=179) | 51% local recurrence rate, 53% long-term survival rate (follow up: mean 62 months) | |
| | US, n=11, 1958-1990 | Parathyroidectomy alone (n=3); parathyroidectomy and resection of thyroid/ thymus (n=8) | 3/3 of parathyroidectomy alone experienced recurrence; 1/8 parathyroidectomy plus resection showed recurrence. | Shortell et al. 1991[275] |
| | Retrospective review, Canada, n=10, mean age 53 years, 50% female, 1958-1996 | En bloc resection (4 neck dissection or lymph node sampling, 3 limited surgery) (n=7); adjuvant radiation therapy for microscopic residual disease (n=6). | 7/7 en bloc resection- no evidence of recurrence and achieved normal serum calcium. Adjuvant postoperative radiotherapy: no evidence of local recurrence, and improved disease-free survival in 6/6 patients at 12-156 month (average 62.3 months) follow-up. Remaining 3 had metastatic disease. | Chow et al. 1998[258] |
| | Retrospective review, US, n=57 surgical resection only, n=4 surgery plus adjuvant radiation therapy, n=4 radiation therapy only; follow up period 8.4-358 months (median 75.6 months) | En bloc resection (4 neck dissection or lymph node sampling, 3 limited surgery) (n=7); adjuvant radiation therapy for microscopic residual disease (n=6). | 44% developed disease progression median 27.1 months post surgery; 100% of adjuvant postoperative radiation therapy: free of disease at last follow-up; 100% of radiation therapy only achieved locoregional control. | Munson et al. 2003[272] |

In the SEER cancer registry (1988-2010), of 405 parathyroid carcinoma patients identified, 81.2% underwent parathyoidectomy, 10.4% bloc section, and 1.7% debulking. Histologically the tumors were identified as neoplasms in 2.5%, carcinomas (not otherwise specified) in 95.1%, and adenocarcinomas (not otherwise specified) in 2.5%.[259]

The overall survival directly correlates with margin status of initial resection.[256] Villar-del-Moral and colleagues reported that prognosis for parathyroid carcinomas was heavily dependent on the surgeon's skill, and that the greatest predictive variable for recurrence was intraoperative tumor rupture.[276] Munson and colleagues compared surgery and radiation therapy and reported that the institution at which the initial surgery was performed was a predictor of cause-specific survival.[272]

So far, no single marker can be used to identify malignant parathyroid carcinomas. However, the tumor suppressor *CDC73* (also know as parafibromin) is mutated in HPT-JT syndrome, and is inactive in 67% of sporadic parathyroid carcinoma samples.[256] Table 5.6 shows the symptoms and outcomes of en bloc resection from a 2014 report of HPT-JT in 7 unrelated families, with 5 germline *HPRT2/CDC73* mutations.[277] Other oncogenes or tumor suppressor genes identified in small cohorts of tumor samples include those for cyclin D1 (PRAD1), retinoblastoma (RB), p53, and BRCA2.[256]

Currently there is no effective adjuvant chemotherapy for parathyroid carcinomas, and the best available therapy is complete surgical resection.[260] In cases of recurrence, reoperation is palliative rather than curative, as relapse is likely; the aim is to reduce tumor load and normalize serum calcium levels. Patients requiring repeat operations

**Table 5.5**

**Number of patients receiving treatment for parathyroid carcinomas, US.**

| DATA SOURCE | POPULATION | TREATMENT | PREVALENCE (%) |
|---|---|---|---|
| SEER database, 1988-2003 | US, parathyroid carcinoma (50% female) (n=224) | **Surgery** | |
| | | Simple parathroidectomy | 78.6 |
| | | En bloc resection | 12.5 |
| | | No surgical treatment | 4 |
| | | Other (debulking surgery or unspecified) | 4.9 |
| | | **Radiation therapy** | |
| | | Postoperative radiation therapy | 9.4 |
| | | Radiation therapy (without surgery) | 0.4 |
| | | No radiation therapy | 90.2 |
| | | **Other** | |
| | | No treatment | 3.6 |

Source: Lee et al. 2007[264]

**Table 5.6**

**Hyperparathyroidism-jaw tumor (HPT-JT) syndrome symptoms, recurrence and survival, US.**

| DATA SOURCE | METHOD | POPULATION | SYMPTOMS | PREVALENCE (%) OR SURVIVAL (YEARS) |
|---|---|---|---|---|
| Review of patients at NIH Warren Mangnuson Clinical Center; July 1986-January 2014 | Retrospective analysis | US, 7 unrelated families; 15/16 patients underwent en bloc resection; median age 30.7 years; median follow-up 7.4 years | Multiglandular | 31% |
| | | | Parathyroid carcinomas | 37.5% |
| | | | Biochemical recurrence | 20% |
| | | | Overall survival (median) | 8.9 years |

Source: Mehta et al. 2014[277]

have a 60% lifetime accumulated surgical risk.[256,260] Due to the rare nature of parathyroid carcinomas, there are often not enough patients for clinical trials, and studies have not been successful. A few reports indicate short-term remission from use of synthetic estrogens and decarbazine, albeit in very few patients.[256,260,270]

# 6 PHEOCHROMOCYTOMAS AND PARAGANGLIOMAS

Pheochromocytoma (PHEO) and paraganglioma (PGL) are rare neuroendocrine tumors of the autonomous nervous system, which arise in adrenal and extra-adrenal glands respectively, and occur individually or together and are often catecholamine-secreting.[199,211,278]

PHEO and PGL syndromes are most commonly associated with either succinate dehydrogenase (SDH) gene-related hereditary PGL syndrome, MEN2A and MEN2B, neurofibromatosis 1 (NF-1) or Von Hippel-Lindau disease (VHL) syndromes (Table 6.1).

Hereditary PHEO and PGL syndromes are linked to germline mutations in the *SDH* gene subunits *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, *SDHA*, and in *TMEM127* and *MAX*, respectively (see Table 6.1).[219,279] The specific gene mutations and the primary characteristics associated with hereditary PHEO and PGL syndromes are shown in Table 6.1.

The majority (70-75%) of PGL/PHEOs occur sporadically, and genuine sporadic cases are confirmed by the exclusion of germline mutations. Sporadic PHEOs are unicentric, unilateral, and diagnosed later in life than familial cases that are multicentric and bilateral.[210] The aetiology of sporadic PGL/PHEO tumors is unknown but thought to be specific alterations in multiple genes. In a 2000 study from the Netherlands, the cause of tumors in PHEO cases (n=29) was speculated to be loss of heterogeneity and possibly involvement of tumor suppressor genes with losses most frequently observed on chromosomes 1p (86%), 3q (52%), 6q (34%), 3p, 17p (31%), 11q (28%), and gains on 9q (38%) and 17q (31%). Malignancy was associated with deletions on 6q (60%

**Table 6.1**

**Primary characteristics and genetic mutations linked to pheochromocytomas (PHEO) and paragangliomas (PGL).**

| PARAGANGLIA (PGL) / PHEOCHROMOCYTOMA (PHEO) SYNDROMES | PRIMARY CHARACTERISTICS | GENETIC MUTATIONS | REFERENCES |
|---|---|---|---|
| PGL syndrome type 1 | PGL and PHEO | *SDHD* | Almeida and Stratakis. 2010[199]; Kantorovich et al. 2010[233]; Chetty. 2010[234] |
| PGL syndrome type 2 | PGL | *SDHAF2 (SDH5)* | Kantorovich et al. 2010[233] |
| PGL syndrome type 3 | PGL | *SDHC* | Almeida and Stratakis. 2010[199]; Kantorovich et al.[233]; Chetty. 2010[234] |
| PGL syndrome type 4 | PGL and PHEO | *SDHB* | Almeida and Stratakis. 2010[199]; Kantorovich et al. 2010[233]; Chetty. 2010[234] |
| PGL syndrome type 5 | PGL | *SDHA* | Karasek et al. 2013[208]; Kirmani and Young. 2008[211] |
| MAX-related syndrome | PHEO, possibly PGL | *MAX* | Kirmani and Young. 2008[211]; Burnichon et al. 2012[219] |
| TMEM127-related syndrome | PHEO | *TMEM127* | Kirmani and Young. 2008[211]; Qin et al. 2010[235] |
| Carney-Stratakis syndrome or Carney-Stratakis dyad (subcategory of SDHx-related PGL) | Extra-adrenal PGL, and gastrointestinal stroma tumors | *SDHA, SDHB, SDHC, SDHD* | Kirmani and Young. 2008[211]; Almeida and Stratakis. 2010[100] |

Abbreviations: PHEO, pheochromocytoma; PGL, paraganglioma.

malignant, 21% benign) and 17p (50% malignant, 21% benign).[280] One 2006 study suggested that chromosome 1p (the most common genetic alteration in sporadic PHEO), was the site of multiple tumor suppressor genes and another study suggested that a region on 22q was also involved.[281, 282]

A genome-wide high-resolution analysis of 36 sporadic benign PHEOs, showed the loss of a region on chromosome 1p with/without a concomitant loss on 3q in 56% of cases and a second abnormality on 3p with/without concomitant loss on 11q (similar to MEN2-related PHEO) in 31% of cases (similar to VHL-related PHEO). Additional losses on 22q were also reported.[283]

## 6.1 PREVALENCE AND INCIDENCE

The worldwide incidence of PGL and PHEO is shown in Table 6.2. A 2010 literature search by Waguespack and colleagues reported that up to 20% of PGL/PHEO tumors were identified in children, and were more frequently familial, bilateral, multifocal, and malignant, relative to those in adults.[248 284]

Traditionally, ~ 10% of PHEO cases were thought to be inherited, however, it is currently estimated that in fact one-third of cases may have a genetic predisposition.[210,285] In a series of 71 patients with PHEO and/or PGL in Italy, 28% were inherited/familial cases. Of these inherited cases, 11% (n=8) had originally been misdiagnosed as apparently sporadic cases.[286] In another study of 329 patients in Spain, germline mutations were detected in 14%, and found at a higher prevalence in PGL (28.7%) than PHEO (4.5%). Somatic mutations were detected in 43% of patients, with a higher prevalence in PHEOs (48.5%) than in PGLs (32.3%). Both these studies recommended prioritizing genetic screening.[287]

Sporadic PGL and PHEO cases combined have an incidence between 0.3 and 1 per 100,000.[285,288,210,279] Up to 0.4% of patients with hypertension have PHEO.[210] In a study of 190 PHEO/PGL cases (1993-2008), 127 of the 202 tumors were apparently sporadic, with no identifiable mutations, while somatic mutations in *VHL* or *RET* genes were identified in 14% of cases.[215]

Approximately 25-30% of apparently sporadic cases of PGL and PHEO have been linked to germline or somatic mutations in the genes *RET*, *VHL*, *NF1*, *MAX*, *HIF2A*, *HRAS* and *BRAF*. The prevalence of detectable mutations has increased in recent years due to improved detection sensitivity with newer technologies such as next-generation sequencing (NGS). In 2015, Luchetti and colleagues identified a number of novel somatic mutations in PHEO and PGL by sequencing mutation hotspots in 50 known human cancer genes. Overall, 8.9% of sporadic cases had *HRAS*/*BRAF* mutations in PHEO/PGL.[289] The three main studies reported a prevalence of 5.5% in all PHEO/PGL (n=438), 8.9% in sporadic PHEO/PGL (n=269), and 9.9% in sporadic PHEO (n=233), respectively.[278,289,290]

In a 1998 retrospective study from Spain, sporadic patients with MEN2A PHEO had later age at presentation (47 years +/- 16 years) than familial cases (38 years +/- 11 years). All sporadic cases were unilateral while familial cases were bilateral.[291]

Somatic mutations in the RET proto-oncogene were identified in up to 31% of benign sporadic PHEO cases. In a 1998 study of 29 malignant and 27 benign paraffin-embeded tissue samples of PHEO cases, a mutation was detected in 1 in 29 malignant and 4 of 27 benign tumors. The mutations were not associated with aggressive tumors in sporadic PHEO.[292]

## 6.2 COST BURDEN OF DISEASE

Due to the rarity of PHEO and PGL syndromes, cost benefit and cost-effectiveness analyses are not available.

**Table 6.2**

**Incidence of familial PGL/PHEO, from literature reviews, worldwide.**

| DISEASE | ANNUAL INCIDENCE (PER MILLION) | REFERENCES |
|---|---|---|
| PGL/PHEO | 3-8 | Kirmani and Young. 2008[211]; Kantorovich et al. 2010[233]; Lefebvre and Foulkes. 2014[210] |
| PHEO | 2-8 | Lefebvre and Foulkes. 2014[210] |
| PGL* | 0.5 | |

Abbreviations: PGL, Paraganglioma; PHEO, Pheochromocytoma.

Note: *, Includes head-and-neck PGL (HNPGL), abdominal PGL, pelvic PGL.

6.3

## DEMOGRAPHIC DIFFERENCES

In general, it is important to note that although gender differences may exist with regards to associated tumor risks, most studies are small and may be influenced by small sample sizes and ascertainment bias.

A South Korea study evaluating 23 male and 35 female PHEO patients reported more headaches, dizziness, anxiety, tremor, weight change, numbness and energy-level changes in females than in males, but no significant difference between the sexes in biochemical phenotypes.[293]

Retrospective studies of asymptomatic PHEO have shown no demographic differences or differences in pathological characteristics in sporadic tumors.[294,295] No demographic differences were detected in a 2013 study (SEER database, 1988-2009) of 287 patients with malignant PHEO and 221 with malignant PGL from the SEER database. However, PHEO appeared to present more aggressively, and more likely to present with distant metastases and larger tumors.[296]

6.4

## LIFE EXPECTANCY AND MORTALITY

In the above-mentioned 2013 study of malignant PHEO (n=287) and PGL (n=221) patients, over a 5-year follow-up period, PHEO patients had lower overall survival (54.4%) than PGL patients (73.3%). This was more independently associated with not having surgery for PHEO and having metastatic disease for PGL.[296]

It is recommended that familial PHEO patients have clinical, imaging, and biochemical assessment throughout their lives for recurrence and for other syndromic neoplasms, and sporadic PHEO cases, with a recurrence rate of 17%, also be followed up indefinitely as there is no way of distinguishing between benign and malignant tumors.[295,297,298]

In a study in France of 51 patients with famlial (n=25) or sporadic (n=26) abdominal extra-adrenal PGL, who had been initially operated on, 14% underwent operative resection after a median of 47 months. The estimated incidence of recurrence was 15% at 5 years and 23% at 10 years. The new lesions were ~10-times more likely to be associated with lymph node metastasis than the primary lesion (43% vs. 4%). Vascular invasion, positive nodes and malignancy were more common at reoperation (43% for all three) than the primary surgery (24%, 4%, 8% respectively), while synchronous distant metastasis was found in 4% of primary surgeries, and was absent from reoperations.[299]

6.5

## KEY TRENDS AND HEALTH OUTCOMES

Most PHEO/PGL are benign and can be completely excised by surgery. The effects of catecholamine secretion need to be controlled with α-adrenergic blockers prior to surgery. While PHEO/PGL disorders are rare in children, 10-20% are diagnosed during childhood, with an average age of 11 years. Early detection (and confirmation by genetic testing if in a familial context) and treatment by a multidisciplinary team produces the best outcomes.[248]

For metastatic disease, meta-iodobenzylguanidine (MIBG) therapy had limited results, although all patients were alive after median follow-up of 5 years.[300,301] Chemotherapy, traditionally a regimen of cyclophosphamide, vincristine, and dacarbazine (CVD) can aid in tumor regression and symptom relief, but does not prolong overall survival. More recently, targeted therapies such as tyrosine kinase inhibitor sunitinib appear to hold more promise. Medical records (December 2007-December 2011) of 17 patients with progressive metastatic PHEO/PGL (including 8 with apparently sporadic tumors) treated with sunitinib were retrospectively reviewed. Of the 17 patients, 47% showed reduced tumor size or disease stabilization (median PFS of 4.1 months). Most of the patients that experienced no treatment benefits had sporadic tumors.[302]

An adrenalectomy is the most common treatment for unilateral tumors in PHEO. Pre-operation treatment includes α- and β-adrenoceptor antagonists, calcium channel blockers, and/or drugs that inhibit catecholamine synthesis to prevent hypertensive crisis during surgery. Usually, phenoxybenzamine, a non-competitive α-receptor blocker is administered. In some cases β-blocking agents or calcium channel blockers may be used prior to surgery.[242]

In a 2009 study from Japan, of 32 patients with metastasized malignant PHEO, primary tumors had been surgically excised in 25. The 50% survival rate in the 32 patients was estimated at 14.7 years. Younger patients had a longer survival. Of the 25 patients, 16 were treated with CVD and 9 were untreated. The survival rate was

worse in the CVD group than in the untreated group, when diagnosed after metastases. Being female and an adrenal origin of tumor were negative factors for CVD chemotherapy.[303] Treatments and outcomes for PGL and PHEO are highlighted in Table 6.3.

# 7 PANCREATIC NEUROENDOCRINE TUMORS

Neuroendocrine tumors that secrete pancreatic hormones (pNETs), also known as islet cell tumors, are a subgroup of neuroendocrine tumors (NETs) that can arise within the pancreas. These pNETs can be functioning NETs (e.g. insuliomas, gastrinomas, glucagonomas, VIPomas, somatostatinomas) or non-functioning NETs (e.g. PPoma). The primary location of insulomas and glucagonomas is the pancreas, but gastriomas (pancreas, duodenum), VIPoma (pancreas, neural, periganglionic, adrenal), somatostastinoma (pancreas, duodenal/jejuna), GRFoma (pancreas, lung, jejunal, adrenal, foregut, retroperitoneal) are also or primarily found extra-pancreatically.[309]

## 7.1 PREVALENCE AND INCIDENCE

In the general population, the incidence of pNETs is <1 per 100,000, but their prevalence is higher in autopsy samples, which suggests many cases may be subclinical (Table 7.1).[310] Between 10 and 30% of pNETs are functioning, and of these, insulinomas and gastrinomas are the most common sub-types (Table 7.1). Overall gastrointestinal NETs are the second most prevalent malignancy in the GI tract, only surpassed by colon cancer.

In early studies, non-functioning pNETs were thought to present late in the disease course, often when liver metastases is already detectable in 60-85% of cases; however, more recent reports implicate an earlier occurrence of pNETs, during the asymptomatic/preclinical stage, and at a higher frequency than previously reported (Table 7.1).[309]

While most pNETs arise sporadically, less than 10% are associated with one of four inherited syndromes: multiple endocrine neoplasia 1 (MEN1), von Hippel Lindau disease (VHL), neurofibromatosis-1 (NF1), or tuberous sclerosis complex (TSC).[309,311] Prevalence of familial forms of pNETs syndromes are shown in Table 7.2. Inherited cases of pNETs arise at an earlier age than sporadic disease.[309] Approximately 50% of all MEN1 patients develop functioning pNETs by age 50 years, and Zollinger-Ellison syndrome in MEN1 patients develops a decade earlier than in sporadic gastrinomas.[311] Clinical signs of pNET in MEN1 patients are seen in only 20-80% of cases, while microscopic signs of disease are present in 80-100%, suggesting that there are many asymptomatic cases.[311]

A number of methods for imaging analysis of pNETs have similar sensitivities: CT (62-83%), magnetic resonance imaging, MRI (85-100%), somatostatin receptor scintigraphy, SRS (75-100%), positron-emission tomography, PET (94-100%), and endoscopic ultrasonography, EUS (82%).[311] While CT and MRI can identify 30-66% of insulinomas, endoscopic ultrasonography and EUS show a higher sensitivity for detecting insulinomas and are also more useful in identifying small tumors than CT and MRI. CT/MRI, octreotide scan and endoscopic ultrasound can be used to detect gastrinomas, glucagonomas and VIPomas.[317]

Recently, next generation sequencing (NGS) has been used to identify the frequency of novel somatic gene mutations associated with pNET (Table 7.3).

## 7.2 DEMOGRAPHIC DIFFERENCES

Demographic data for pNETs is limited; however, they are reported to be more common in Caucasians (84%), and in males (55%).[311] The mean age at onset for pNETs is 55.2 years for functioning tumors, and 58.8 years for nonfunctioning tumors. The overall pNET incidence per 100,000 increased with age from 1 at 15-19 years, to peak at 76 at age 70-79 years, and reflected that of non-functional pNETs.[318]

## 7.3 LIFE EXPECTANCY AND MORTALITY

In 2013, Ter-Minassian reported that of the 900 neuroendocrine tumor patients at a single institute, 23% had pNET with a 5-year disease-free survival rate of 57%, and a median disease-free survival of 5.8 years. The median duration before diagnosis was 3.4 months, with 19.5% reporting durations of 1-5 years, 2.5% of 5-10 years, and 2% of >10 years. The overall survival was related to the tumor site: with small bowel NET patients showing double the survival duration of pNET (Table 7.4).

**Table 6.3**

**Outcomes of treatments for paraganglioma and pheochromocytoma syndromes.**

| PARAGANGLIOMA (PGL)/ PHEOCHROMOCYTOMA (PHEO) SYNDROMES | TREATMENT | OUTCOME | REFERENCES |
|---|---|---|---|
| PGL/PHEO | 121 patients (75% sporadic tumors, 16% MEN2-related tumors, von Recklinghausen's disease in 9%) surgically treated over 47 years; in one referral center in Sweden, 1950-1997. | Patients successfully treated for PHEO/PGL still have higher mortality than the general population. Over 15±6 year observation, 42 patients died vs. 23.6 in general population. 85% hypertensive at diagnosis, and >50% still hypertensive 1 year after surgery. No intra- or post-operative mortality. | Khorram-Manesh et al. 2005[304] |
| PGL/PHEO | 221 patients with malignant PGL, 287 patients with malignant PHEO, US, SEER 18, diagnosed 1988-2008. Surgery had been performed in 74.3% of PHEO and 78.9% of PGL; external beam radiation administered in 8% PHEO and 28.1% PGL. | Lower overall survival for PHEO (54%) than PGL (73.3%); disease-specific survival were similar for PHEO (73.5%) and PGL (80.5%); the 5-year overall and disease-specific survival rates were 58.1% and 71.1% for PHEO, and 80% and 86.3% for PGL. Metastasis at diagnosis and failure to undergo surgery compromised survival. | Goffredo et al. 2013[296] |
| metastatic PHEO/PGL | 123I-MIBG treatment for ~30% of patients who respond to scintigraphy. | Biochemical response rates up to 67% and symptom response rates up to 89%. To be proven in multicenter studies. | Chen et al. 2010[279]; Gedik et al. 2008[305] |
| | Chemotherapy: combination cyclophosphamide, vincristine, and dacarbazine (CVD), especially if rapidly growing tumors. | Temporary tumor regression and symptom relief in up to 50% of patients; response rates in ~30% of patients | Chen et al. 2010[279]; Averbuch et al. 1988[306] |
| Metastatic PHEO or sympathetic extra-adrenal PGL (excluding HNPGL) | Systemic chemotherapy (doxorubicin or non-doxorubicin-based or other-platins; cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone or prednisolone; temozolomide; etoposide; imatinib; ifosfamide; and thalidomide), patients (n=52) diagnosed January 1979-March 2010. The University of Texas MD Anderson Cancer Center. | 33% responded to front-line chemotherapy (treated with cyclophosphamide and dacarbazine), 17% had reduced tumor size, 8% had normalized blood pressure and 8% had both. The OS response rate was 51% at 5 years in all 52 patients. In the 33% that were chemotherapy-responsive, median OS time was 6.4 years and for non-responders it was 3.7 years. Patients who had surgery for primary tumor and chemotherapy, had survival of 6.5 years compared with 3 years for those with chemotherapy only. None of the 4 patients with *SDHB* mutations responded to chemotherapy. 1 patient with *SDHC* mutation did respond to treatment. | Ayala-Ramirez et al. 2012[307] |
| PGL | Operative excision of EAPs can lead to prolonged remission, sporadic (n=26) and inherited (n=25) EAPs, France. | Local regional recurrence of 15% at 5 years, 23% after 10 years; all were secreting; 38% provoked clinical symptoms. New lesions were smaller than primary EAP and more associated with lymph nodes (43% vs. 4%). Operative excision complete in n=5 and clinical remission maintained in n=4 after a 57 month follow-up. | Van Slycke et al. 2009[299] |
| PHEO: organ-contained and unilateral | Open surgery and laparoscopic procedures in a large institutional patient series (n=101) in India with large (>6cm) PHEOs, 1990-2010. | While cure and hypertension outcomes were no different, morbidity was more frequent in open surgery (n=12) than laparoscopic patients (n=4). | Agarwal et al. 2012[308] |

Abbreviations: PGL, paraganglioma; PHEO, pheochromocytoma.

Table 7.1

| Prevalence and incidence of pancreatic neuroendocrine tumor (pNET) subtypes and syndromes, worldwide. | | | |
|---|---|---|---|
| PANCREATIC NEUROENDOCRINE TUMOR SUBTYPES AND SYNDROMES (pNETS) | DATA SOURCE | POPULATION | HORMONE |
| pNETS | SEER database | US | N/A |
| | Literature review | Worldwide, Pancreatic tumors | N/A |
| | Literature review | Worldwide, Neuroendocrine tumors | N/A |
| | Literature review | Worldwide, autopsy studies | N/A |
| **Non-functioning pNET** | | | |
| | Literature review | Worldwide | None |
| **Functioning pNETs** | | | |
| Gastrinoma | Literature review | Worldwide | gastrin |
| Insulinoma | Literature review | Worldwide | Insulin |
| VIPomas | Literature review | Worldwide | Basoactive intestinal peptide |
| Glucagonoma | Literature review | Worldwide | Glucagon |
| Somatostatinoma | Literature review | Worldwide | Somatastatina |
| ACTHomas | Literature review | Worldwide | Adrenocorticotropic hormone (ACTH) |
| pNET causing carcinoid syndrome | Literature review | Worldwide | Serotonin Tachykinins |
| pNET causing hypercalcemia | Literature review | Worldwide | PTHrP |

Abbreviations: N/A, not applicable; N/G, not given.

| FUNCTIONING SYNDROME | INCIDENCE (PER 100,000 PER YEAR) | PREVALENCE OF ALL PNETS (%) | PREVALENCE OF FUNCTIONING PNETS (%) | REFERENCES |
|---|---|---|---|---|
| N/A | 0.43 | N/G | N/A | McKenna and Edil. 2014[311] |
| N/A | N/G | 1–4% | N/G | McKenna and Edil. 2014[311]; D'Haese et al. 2014[312]; Milan and Yeo. 2012[313] |
| N/A | N/G | 7% | N/G | McKenna and Edil. 2014[311] |
| N/A | N/G | 0.8–10% | N/G | Ito et al. 2012[309] McKenna and Edil. 2014[311]; Berge et al. 1976[314] |
| | | | | |
| Pancreatic polypeptideomas (PPomas): non-functioning-pNET | 1-3 | N/G | N/G | Ito et al. 2012[309] |
| | | | | |
| Zollinger-Ellison syndrome (ZES) | 0.5-1.5 | N/G | 16–30% | McKenna and Edil. 2014[311]; Ito et al. 2012[309] |
| Insulinoma | 1-3 | N/G | 35–40% | Ito et al. 2013[309]; McKenna and Edil. 2014[311] |
| Verner-Morrison syndrome, Pancreatic cholera, WDHA syndrome | 0.05-0.2 | N/G | <10% | Ito et al. 2012[309]; McKenna and Edil. 2014[311] |
| Glucagonoma | 0.01-0.1 | N/G | <10% | Ito et al. 2012[309]; McKenna and Edil. 2014[311] |
| Somatastatinoma | <0.1% | N/G | <5% | Ito et al. 2012[309]; McKenna and Edil. 2014[311] |
| ACTHoma | <0.1% | N/G | N/G | Ito et al. 2012[309] |
| PET causing carcinoid syndrome | <0.1% | N/G | N/G | Ito et al. 2013[315] |
| PTHrPoma | <0.1% | N/G | N/G | Ito et al. 2012[309] |

Table 7.2

| Prevalence of familial pancreatic neuroendocrine tumor (pNET) syndromes from literature reviews, worldwide. | | | | |
|---|---|---|---|---|
| FAMILIAL PNET SYNDROME | PREVALENCE (PER 100,000 POPULATION) | PREVALENCE OF PNETS IN THE FAMILIAL PNET SYNDROME | PREVALENCE OF PNET SUBTYPE (%) | REFERENCES |
| MEN1 | 1-10 | Gastrinomas | 54 | Ito et al. 2012[309]; McKenna and Edil. 2014[311]; Sadowski and Triponez. 2015[316] |
| | | Insulinomas | 18 | |
| | | Glucagonomas | 3 | |
| | | Vipomas | 3 | |
| | | GRFomas and Ssomas | <1 | |
| von Hippel-Lindau disease (VHL) | 2-3 | Single non-functioning pNET (98%) | 10-17 | Ito et al. 2012[309]; McKenna and Edil. 2014[311] |
| Neurofibromatosis-1 (NF-1) (Von Recklinghausen disease, VRH) | ~25 | Duodenal Ssomas, Rare pNETs | 0-10 | Ito et al. 2012[309]; McKenna and Edil. 2014[311] |
| Tuberosis sclerosis (TSC) | 10 | Uncommon | Rarely develop functioning pNETS, non-functioning pancreatic endocrine tumors (PET) | Ito et al. 2012[309]; McKenna and Edil. 2014[311] |

Note: *, includes Head-and-neck PGL (HNPGL), abdominal PGL, pelvic PGL.

Table 7.3

| Frequency of genetic mutations associated with pNETs, worldwide. | |
|---|---|
| GENE | MUTATION FREQUENCY (%) |
| *MEN1* | 44 |
| *DAXX* | 25 |
| *ATRX* | 18 |
| *mTOR* | 16 |
| Source: McKenna and Edil. 2014[311] | |

The authors also concluded that while most cases were diagnosed soon after clinical onset, prolonged time from onset to diagnosis was common.[319]

Ter-Minassian and colleagues in 2013 reported statistical bias for shorter survival times in pNET patients (at a single institute) than those with small bowel carcinoids (Table 7.4). The authors suggested that most studies overestimated survival time because of variability in times of patients entering a study after diagnosis.[319]

Approximately 21% of patients presenting with pNETs have locally advanced disease, while 60% have metastatic disease.[311,320] The chance of pNETS (except insulinomas) becoming malignant is estimated to be ~50%.309 pNETs are the most common underlying cause of MEN1-associated mortality.[316] MEN1 patients have a 50% 15-year survival rate for metastatic gastrinomas. Small tumors (<2cm) have no difference in life-expectancy compared to MEN1 with no pNETS.[311]

In a retrospective study of 324 patients with pNETs, Ekeblad and colleagues reported a mean overall survival of 8.25 years, a 5-year survival rate of 64%, and a 10-year survival rate of 44%. While hereditary and non-functioning tumors were not associated with poor prognosis, tumor staging was associated (Table 7.5).[321] Similarly, Wang and colleagues reported that resectability did not influence long-term survival for functioning or non-functioning pNETS (Table 7.5), and that prognosis was dependent on functioning status of the tumor, tumor stage, lymph node status, and pathological classification.[322]

## 7.4 KEY TRENDS AND HEALTH OUTCOMES

Diagnosis and treatment for NETs involves multidisciplinary teams for diagnosis, surgery, surveillance, chemotherapy, and targeted therapies.[311,316,329] Familial disorders are more complicated to diagnose and treat

than sporadic ones because of their earlier presentation and the presence of multiple tumor sites.[311,315,316] Serotonin is secreted by ~70% of tumors in jejunum, ileum, proximal colon and appendix, but is uncommon in pNETs; and secreted by 10-35% of NETs in the stomach and respiratory tract. In some cases, measurement of Chromogranin A or serotonin in blood, or its breakdown product 5-hydroxyindoleactic acid (5-HIAA) in urine, can assist in diagnosis but low sensitivity and false positives are problematic, and new circulating biomarkers such as the NETest are being developed.[329] As 90% of tumors are not associated with hypersecretion of hormones or peptides (non-functioning), the first recognizable symptom (the tumor mass) is usually identified later in disease progression.[329] Additionally, with increased imaging, pNETs are increasingly found incidentally and observation (rather than surgery) has become a reasonable choice for small pNETs (<2cm). Detecting functioning tumors is also problematic; the hypersecretion of hormones can produce syndromes that mimic other disorders, potentially delaying correct diagnosis.[329] Treatments for functioning NETs must control hormone excess as well as the tumor.[311,329,330] In all cases of localized tumors, surgical resection should be offered, and if inoperable or in cases of metastases, combination therapy with surgical debulking, medical therapy to control hormone secretion and tumor growth are the treatments of choice. Table 7.6 summarizes health outcomes of treatment strategies for pNETs.

Current standard of care strategies for NETs are outlined in Table 7.7. Surgery is the first-line therapy when NETs are resectable, and is also recommended for debulking of liver metastases and correction of cardiac valvular disease.[311,329] Although surgery is the primary treatment, pNETs are more sensitive to chemotherapy than other NETs such as carcinoid tumors.[311] The therapeutic approaches available for NET metastatic disease, advanced pNET, and carcinoids include surgery, radiotherapy, targeted molecular therapy and chemotherapy (Table 7.8). New cytotoxic agents namely taxanes, gemcitabine, pemetrexed, and topotecan have not been as successful, showing response rates under 10%.[329] On February 26th 2016, the FDA approved the use of Afinitor (everolimus) in adult patients with progressive, non-functional gastrointestinal and lung NETs that are unresectable, locally advanced or metastatic (Table 7.8).[331,332]

**Table 7.4**

**Comparison of survival rates for neuroendocrine tumors (NETs).**

| DATA SOURCE | METHOD | POPULATION | SITE OF NEUROENDOCRINE TUMOR | PERCENTAGE OF COHORT (%) | 5-YEAR DISEASE-FREE SURVIVAL RATES (%) | MEDIAN DISEASE-FREE SURVIVAL (YEARS) | MEDIAN ESTIMATED OVERALL SURVIVAL FOR METASTATIC PATIENTS (YEARS) | MEDIAN SURVIVAL DURATION FOR METASTATIC PATIENTS * (YEARS) |
|---|---|---|---|---|---|---|---|---|
| Gastrointestinal clinic at Dana-Farber Cancer Institute (DFCI) 2003-2010. Medical records or social security death index, | Prospective Institutional database study | US, patients with resected, localized disease (n=354) | All | 100 | 56 | 5.8 | 8.0 | 5.2 |
| | | | Small bowel NET | 38 | 57 | 5.8 | 10.1 | 7.9 |
| | | | Pancreatic NET (pNET) | 23 | 42 | 4.1 | 5.9 | 3.9 |
| | | | Other site NETs (unknown primary site, bronchi, appendix, stomach, other origins) | 39 | N/G | 7.3 | 5.9 | 3.7 |

Source: Ter-Minassian et al. 2013[319]

Abbreviations: N/G, not given.

Note: *, calculated using modified Kaplan-Meier analysis that corrects for immortal time bias or left truncation bias in institutional databases.

**Table 7.5**

**Survival rates for patients with neuroendocrine tumors (NETs), worldwide.**

| DATA SOURCE | POPULATION | NEUROENDOCRINE TUMORS | 5-YEAR SURVIVAL RATE (%) | 10-YEAR SURVIVAL RATE (%) | REFERENCES |
|---|---|---|---|---|---|
| Literature reviews | Pancreatic endocrine tumors (pNETs) | Untreated liver metastases in patients with nonfunctioning pNET | 30–40 | | McKenna et al. 2014[311]; Ehehalt et al. 2009[323] |
| | | After hepatic surgery of patients with nonfunctioning pNET metastases | 47-76 | | |
| SEER 13 database, 1973-2000 | adults age≥18 years (44.8% female) overall survival (n=1,483) | Functioning pNETs | 47.6 | 33.7 | Halfdanarson et al. 2008[318]; Ehehalt et al. 2009[323] |
| | | Nonfunctioning pNETs | 31.3 | 17.0 | |
| Mayo Clinic, Rochester 1927-1986 (60-year study) | US, age range 8-82 years, median age 47 years (59% female) (n=224) | All functioning insulinoma | | 88 | Service et al. 1991[324]; Ehehalt et al. 2009[323] |
| | | Malignant insulinoma (5.8%) | | 29 | |
| Retrospective review of patients treated at Department of Surgery, University of Vienna, Austria | Austria, mean age at operation 49.5 years, range 12-80 years, pNET surgically treated (n=100) | Insulinoma | 97 | | Schindl et al. 2000[325]; Ehehalt et al. 2009[323] |
| | | Gastrinoma | 50 | | |
| National Institute of Health, December 1981- August 1998 | Zollinger-Ellison syndrome or malignant gastrinoma patients who underwent laparotomy, (n=151): sporadic gastrinomas (n=123); MEN1 (n=28); mean follow up 8 ±4 years. DFS = disease-free survival; DSS = disease-specific survival | Sporadic gastrinoma | 40 (DFS); 100 (DSS) | 34 (DFS); 95 (DSS) | Norton et al. 1999[326] |
| | | MEN1 | 4 (DFS) 100 (DSS) | 0 (DFS) 86 (DSS) | |
| Medical records of patients diagnosed and treated at tertiary referral center, retrospective study | Sweden, patients at a single institution; median follow up 54 months (n=324) | pNET | 64 | 44 | Ekebald et al. 2008[321] |

| Survival rates for patients with neuroendocrine tumors (NETs), worldwide. (continued) | | | | | |
|---|---|---|---|---|---|
| DATA SOURCE | POPULATION | NEUROENDOCRINE TUMORS | 5-YEAR SURVIVAL RATE (%) | 10-YEAR SURVIVAL RATE (%) | REFERENCES |
| Literature review | Pancreatic endocrine tumors | Insulinoma | 97 | | Mansour and Chen. 2004[327] |
| | | Gastrinoma | 60-70 | | |
| | | Glucagonoma | 50-60 | | |
| | | VIPoma | 80-90 | | |
| | | Somatostatinoma | 90 | | |
| | | Non-functioning and PPoma | 80-90 | | |
| Cohort study | Taiwan, pancreatic and peripancreatic tumors; n=93 Functional (n=39); Nonfunctional (n=54) | Resectable (disease-specific survival) | 86.4 | | Wang et al. 2011[322] |
| | | Unresectable (disease-specific survival) | 65.6 | | |
| SEER 9 registries, 1975-2006 | children and adolescents, age <30 years (n=1,073) | NETs | 83-84 | | Navalkele et al. 2011[328] |
| | | Malignant carcinoids of appendix, lung, and hindgut | 96-100 | | |
| | children and adolescents, females, age <30 years | NETs of the cervix and ovary only (small cell carcinomas) | 24-29 | | |

Abbreviations: N/G, not given.

Note: *, calculated using modified Kaplan-Meier analysis that corrects for immortal time bias or left truncation bias in institutional databases.

**Table 7.6**

**Health outcomes measures for pancreatic neuroendocrine tumors (pNETs) from literature reviews.**

| PNETS | MALIGNANCY FREQUENCY | HORMONE-RELATED SYMPTOMS | TREATMENT | OUTCOME | REFERENCES |
|---|---|---|---|---|---|
| Gastrinomas (Zollinger-Ellison syndrome) | 60–90% | Peptic ulcer or GERD | Need surgical resection for all pNET types Proton-pump inhibitors for acute and long-term control (including omeprazole, olansoprazole. | >98% effective | Ito et al. 2013[315]; McKenna and Edil. 2014[311]; Ehehalt et al. 2009[323]; Ramage et al. 2012[329] |
| Insulinomas | 5–15% | Hypoglycemia | Surgical resection | Surgery successful in >95% of cases | Ito et al. 2013[315]; McKenna and Edil. 2014[311]; Sadowski and Triponez. 2015[316] |
| | | | Diazoxide inhibits insulin release | Hypoglycemia controlled in 50-60% of patients | |
| VIPomas | 70–90% | Severe diarrhea, leads to dehydration and hypokalemia | Long-acting somatostatin analogues: octreotide-LAR, lanreotide-autogel | Diarrhea controlled in >90% of patients | Ito et al. 2013[315]; McKenna and Edil. 2014[311]; Burns and Edil. 2012[330]; Ramage et al. 2012[329] |
| Glucagonoma | 60–75% | Dermatitis, diabetes, diarrhea, deep vein thrombosis | Long-acting somatostatin analogues: octreotide-LAR, lanreotide-autogel | Life-threatening skin lesion necrolytic migratory erythmia (NME) controlled in 50-90%, improvement in weight loss, abdominal pain, diarrhea, diabetes does not improve | Ito et al. 2013[315]; Burns and Edil. 2012[330]; Ramage et al. 2012[329] |
| | | Hypoglycemia | Diazoxide | Hypoglycemia controlled in 50-60% of patients | Ito et al. 2013[315] |

**Table 7.7**

| Health outcome measures for current standards of care for neuroendocrine tumors (NETs) from literature reviews. | | | |
|---|---|---|---|
| DISEASE | THERAPEUTIC STRATEGY | OUTCOME | REFERENCES |
| NETs | Lung resection | 67-96% 5-year survival, depending on histology and lymph node involvement; 5-year survival 87%, post-operative mortality 6% | Ramage et al. 2012[329] |
| | Liver resection | Liver metastases curative in ~10% of cases, if confined to single lobe | |
| | Liver transplant for end-stage NET and uncontrollable symptoms, and unresponsive to other therapies | Highest disease-free survival up to 77% at 1-year; actural disease-free survival 62% at 1-year and 23% at 5 years | |
| Liver metastases | Surgery if debulking of >90% of the tumor is possible: only 5-15% of patients are candidates | Debulking of >90% of tumor can extend survival; resolution of symptoms in 96% in one study. Reoperationon recurrence can extend survival up to 70% after 10 years. | McKenna and Edil. 2014[311]; D'Haese et al. 2014[312] |
| Pancreatic neuroendocrine neoplasms (pNENs) | Surgery for curative resection, and to prevent or delay local or metastaic recurrence | Survival benefit of 79 months for resected patients relative to nonresected (114 vs. 35 months) | D'Haese et al. 2014[312] |

**Table 7.8**

| Health outcomes measures for advanced pNETs. | | | | | |
|---|---|---|---|---|---|
| THERAPEUTIC STRATEGY | INDICATION | STUDIES | RESPONSE | SURVIVAL | REFERENCES |
| Chemotherapy | pNET | streptozotocin, 5-fluorouracil and doxorubicin | In a US retrospective series of locally advanced and metastatic pancreatic endocrine carcinomas (n=84); 39% showed tumor response; with median duration 9.3 months | 2-year overall survival rates was 74%; 2-year progression-free survival rate was 41% | Kouvaraki et al. 2004[333]; McKenna and Edil. 2014[311] |
| | | temozolomide + capecitabine | In a single-arm retrospective study of metastatic pancreatic endocrine carcinomas (n=30), tumor response rate was seen in 70% of patients | 2-year survival rate of 92%: median progression-free survival of 18 months; grade 3 or 4 adverse events in 12% | Strosberg et al. 2011[334]; McKenna et al. 2014[311] |
| Peptide receptor radiotherapy (PPRT) | Gastroenteropancreatic NETs | Lu-177 labelled | Complete tumor response in2%; partial tumor response in 28% (n=504) | Minor tumor response (decrease in size by >25% but <50%) in 16%; median time to disease progression 40 months; median overall survival 48 months; median overall survival from diagnosis 128 months; Serious treatment toxicity 3.6%. | Kwekkeboom et al. 2008[335]; McKEnna and Edil. 2014[311] |
| Targeted molecular therapy | Progressing, advanced, or symptomatic pNETs | Everolimus: mTOR signalling inhibitor | US, low-or intermediate grade pNETs with radiologic progression <12 months; n=207 patients, n=203 placebo. 65% reduction in estimated risk of progression/death. 34% of treated patients alive and progression free for 18 months vs. 9% with placebo | Median progression free survival of 11 months for everolimus, 4.6 months for placebo. Stable disease (by RECIST) in 73% for everolimus and 51% for placebo. | Yao et al. 2011[336]; Ramage et al. 2012[329] |
| | | Sunitinib: tyrosine kinase inhibitor targets VEGF receptors | France, phase III trial, n=171, advanced well differentiated pNETs, tumor response rate 9.3% for treatment vs. 0% placebo | Median progression free survival 11.4 months for sunitinib vs. 5.5 months placebo | Raymond et al. 2011[337]; McKenna and Edil. 2014[311] |

Abbreviations: NETs, neuroendocrine tumors; pNETs, pancreatic neuroendocrine tumors.

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