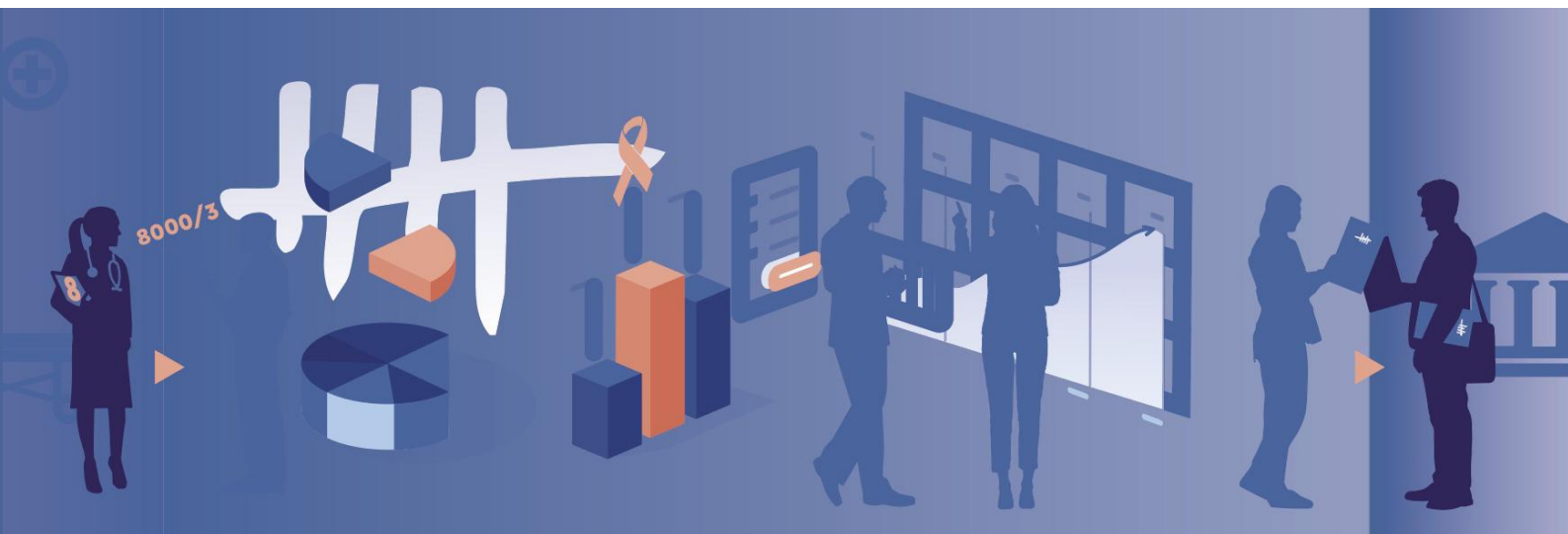


Volume-outcome relationship in cancer care:

ADRENAL CANCER – LITERATURE OVERVIEW





Colophon

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Adrenal cancer

1. Epidemiology

Adrenal cancer is a rare malignancy arising in the adrenal glands, which are located atop the kidneys and produce essential hormones. In 2023, the Belgian Cancer Registry recorded 97 new cases of adrenal cancer, of which 31 occurred in men and 66 in women ¹.

Different types of cancer can arise in the adrenal glands. Adrenocortical carcinoma (ACC) originates in the adrenal cortex, while malignant pheochromocytoma develops from chromaffin cells located in the adrenal medulla. Chromaffin cells are also found in extra-adrenal paraganglia, and tumours arising from these sites are referred to as paragangliomas. Due to their shared cellular origin and overlapping clinical features, the combined term pheochromocytomas and paragangliomas (PPGLs) is commonly used. PPGLs are more common than ACC, with a worldwide estimated incidence of 2-8 cases per million people per year, compared to 0.5-2 for ACC.²

Both ACC and PPGLs can be hormonally active: ACC may lead to excess production of cortisol, aldosterone and sex hormones (e.g. testosterone and androgen (only in women), oestrogen (only in men), dehydroepiandrosterone sulphate (DHEAS)), whereas PPGLs may result in elevated levels of catecholamines. These hormonal excesses can manifest clinically as Cushing's syndrome or trigger life-threatening hypertensive crises, underscoring the importance of early recognition and appropriate management.

Most adrenal tumours are discovered incidentally during radiologic imaging performed for unrelated clinical reasons. The majority of these adrenal incidentalomas are benign and hormonally inactive. However, malignancy and hormonal excess must always be carefully excluded. As imaging techniques become more widely used and increasingly sensitive, the detection rate of adrenal tumours has risen. Despite this, adrenal cancer remains a rare condition which can possibly be life-threatening, requiring specialized multidisciplinary care.

Surgery is the main treatment for non-metastatic ACC and PPGL. For ACC, the best surgical approach is still under debate, with laparoscopic adrenalectomy being arguable for smaller tumours. Additional locoregional lymphadenectomy is recommended (with a minimum of 5 nodes), and adjuvant chemotherapy with mitotane could be considered for patients with high recurrence risk. The use of adjuvant radiotherapy is limited to patients with incomplete resection and/or advanced stages as it only reduces the risk of local recurrence but does not prevent distant recurrences. As a result, adjuvant radiotherapy has little impact on OS. PPGLs can mostly be operated using a minimally invasive approach (laparoscopy, retroperitoneal approach) with extreme caution for perioperative management of hormone and glucose levels, electrolytes and blood pressure. For both tumours, surgery should be performed by an experienced surgeon, given the prognostic importance of achieving complete resection. Moreover, the entire operative team, including anaesthesiologists, must be well trained in adrenal surgery. The management of ACC further necessitates a multidisciplinary approach, involving endocrinologists, surgeons, oncologists, radiotherapists and other relevant specialists to ensure comprehensive patient care.

2-4

2. Aims and scope of the current literature study

The aim of this literature study was to evaluate the evidence for a volume–outcome association in the oncologic care of adrenal cancer. A targeted literature search was conducted in July 2025 using the PubMed and Cochrane Library databases and broad MeSH term searches (e.g. adrenal cancer, volume, cancer, centralisation). The aim was to compile a general overview of the available evidence, with firstly a particular focus on studies that summarize existing data, including (systematic) reviews and meta-analyses. This was further supplemented with more recent individual studies. A full systematic literature review was beyond the scope of the current study.

To guide the selection process, several criteria were established. First, regarding outcomes, the primary focus was on post-treatment mortality and overall survival. Second, evidence related to care concentration across the entire oncologic trajectory was searched, rather than focusing on specific treatment modalities. However, given that surgery is the key part of adrenal cancer treatment, most of the research has concentrated on surgical treatment. Third, for insights into the organisation of adrenal cancer care in other countries, priority was given to studies involving populations most relevant to the Belgian context, specifically those conducted in Europe.

3. Evidence in literature

Since evidence regarding a volume–outcome association in adrenal cancer care may have been previously summarised, an initial search was conducted to identify existing systematic reviews and meta-analyses on this topic. Only one relevant meta-analysis, by Langenhuijsen et al., was found.⁵ This meta-analysis dates already from 2015 and focuses exclusively on ACC and specifically on surgery (section 3.1). Beyond this, the available literature consists primarily of observational cohort studies and narrative reviews. Summaries of two key narrative reviews, by Kazaure et al. and by Mihai et al. are presented below (section 3.2 and 3.3).^{6,7} An accompanying overview table (section 3.4) presents the main observational studies investigating volume-outcome effects in adrenal cancer. For clarification, these scientific study types can be described as follows: meta-analysis (statistical combination of multiple studies), systematic review (systematic overview of the literature), narrative review (descriptive literature overview), observational cohort study (follows a group of people over time without intervention). It is important to note that these studies focus on adrenal surgery, without addressing other treatment modalities such as chemotherapy. Furthermore, many of them include patients undergoing adrenalectomy for adrenal pathology in general, not solely for adrenal cancer.

3.1 Surgical management of adrenocortical carcinoma: impact of laparoscopic approach, lymphadenectomy, and surgical volume on outcomes—a systematic review and meta-analysis of the current literature (Langenhuijsen et al. 2015)⁵

Systematic search

- in June 2015, according to PRISMA guidelines
- Conducted in Ovid Medline, Embase, and the Cochrane Library
- Relevant subject: The influence of surgical volume on oncologic outcomes for ACC surgery
- Four included studies analysed the effect of surgical volume on outcome after surgical treatment of ACC

Overview of the included studies (see also ‘3.4 Overview table’):

- Gratian et al. 2014⁸
- Kerkhofs et al. 2013⁹
- Hermsen et al. 2012¹⁰
- Lombardi et al. 2012¹¹

Main findings

High-volume centres compared to low-volume centres are associated with:

- Lower local recurrence rates
- Lower distant metastases rates
- Longer time to recurrence

Important limitations

- No exact definition of low- and high-volume centres based on reports in the literature; the required numbers of ACC surgeries range from 4 to 20 cases per year per centre.
- Patient and disease heterogeneity
Low level of evidence of selected studies due to patient and disease heterogeneity and heterogeneous surgeon populations

Conclusion

Adrenal surgery performed in high-volume centres is associated with improved patient outcomes.

3.2 Volume-outcome relationship in adrenal surgery: A review of existing literature (Kazaure et al. 2019)⁶

Narrative review

- Conducted in 2019
- Subject: volume-outcome associations in adrenal surgery



Main findings

Surgeon volume-outcome

- High-volume surgeon ≥ 6 adrenalectomies per year
- Improved outcomes compared with low-volume surgeons:
 - Lower complication rates
 - Reduced postoperative mortality
 - Shorter hospital stays
 - Lower hospitalisation costs

Hospital volume-outcome

- Inconsistent definition
- Fewer studies
- Divergent results, but possible benefit for ACC when treated in high-volume hospitals

Limitations

- Lack of uniform volume thresholds across studies
- Most studies are retrospective and based on large administrative databases, which often lack detailed clinical information

Conclusion

Evidence shows the association between surgical volume and outcomes, supporting the selective referral of patients with adrenal tumours to surgeons who do 6 adrenalectomies per year in order to enhance the likelihood of improved perioperative outcomes at a lower health care cost.

3.3 Volume-outcome correlation in adrenal surgery—an ESES consensus statement (Mihai et al. 2019)⁷

Narrative review

- Conducted in 2019
- Subject: volume-outcome associations in adrenal surgery

Main findings

This paper presents a summary of literature reviewed by a working group, which was established by the European Society of Endocrine Surgeons (ESES), resulting in clear recommendations:

- Adrenal surgery should be performed only in centres doing ≥ 6 cases/year.
 - For ACC the threshold is ≥ 12 adrenal operations/year.
- All such centres should have an integrated multidisciplinary team.
- Surgeons should contribute data to EUROCRINE and European Network for the Study of Adrenal Tumors (ENSAT) registries.



3.4 Overview table with the main observational cohort studies

First author	Year	Country	Data source (years)	Patients (n)	High-volume definition	Main findings for high-volume*	Specific limitations**
Stavrakis et al. ¹²	2007	USA	New York & Florida state database (2002)	13997 (576 adrenalectomies) (benign + malign)	Six groups: 1-3 / 4-8 / 9-19 / 20-50 / 51-99 and ≥100 endocrine surgeries (parathyroidectomy and adrenalectomy) per surgeon per year	For adrenalectomies: reduced length of stay (LOS) (p<0.001) and cost (p<0.01)	Surgeon-volume based on number of adrenalectomies and parathyroidectomies.
Gallagher et al. ¹³	2007	USA	Discharge data Florida (1998–2005)	1816 (benign + malign)	≥7/year per surgeon	Reduced LOS (p<0.001)	
Park et al. ¹⁴	2009	USA	HCUP-NIS database (1999–2005)	3144 (benign + malign)	≥4/year per surgeon ≥14/year per centre	Surgeons: reduced complications (p<0.001) and LOS (p<0.001) Centres: reduced LOS (p<0.01)	
Murphy et al. ¹⁵	2010	USA	NIS database (1998–2006)	40363 (benign + malign)	>6/year per centre	Reduced complications (p<0.001; multivar. NS trend: low-V OR 1.30 [0.98-1.71]) NS lower in-hospital mortality (p=0.50, 1.0 vs. 1.3%; multivar. NS: low-V OR 1.26 [0.71-2.25])	
Villar et al. ¹⁶	2010	Spain	National survey (2008)	155 (benign + malign)	≥5/year per surgeon > 9/year per centre	Surgeons and centres: reduced LOS (p<0.0001) Surgeons: reduced complications (p<0.03)	Voluntary participation (response bias), low response rate
Simhan et al. ¹⁷	2011	US	Discharge data New York, New Jersey, Pennsylvania (1996–2009)	8381 (benign + malign)	≥7/year per centre	Reduced in-hospital mortality (p=0.001) and LOS (p<0.001)	Volume based only on data from the year 1996



First author	Year	Country	Data source (years)	Patients (n)	High-volume definition	Main findings for high-volume*	Specific limitations**
Bergamini et al. ¹⁸	2011	Italy	Prospective: Italian Registry of Endoscopic Adrenalectomy database (2000–2009)	833 (benign + malign)	>30 cases per centre	Reduced complications (p<0.001) and conversion rates (p=0.003)	Limited to laparoscopic cases
Greco et al. ¹⁹	2011	Germany	Questionnaire (2003–2009)	363 (benign + malign)	>10/year per centre	Reduced blood loss (p=0.013) and operative time (p<0.001)	Limited to laparoscopic cases
Kazaure et al. ²⁰	2011	USA	HCUP-NIS database (2003-2008)	6416 (benign + malign)	≥4/year per surgeon >6/year per centre	Reduced complications (p=0.04), LOS (p<0.001) and cost (p=0.043)	
Lombardi et al. ¹¹	2012	Italy	Multi-institutional survey (2004-2010)	263 (ACC only)	≥10 patients recruited per centre during survey	Longer time to recurrence (p<0.01), more LN resection (p<0.01), and more adjuvant therapy (p<0.001)	Voluntary participation (response bias)
Hermesen et al. ¹⁰	2012	The Netherlands	Dutch Adrenal Network (DAN) Registry (1965-2007)	149 (ACC only)	DAN centre	Longer OS (81 vs 20 months, p=0.014)	
Kerkhofs et al. ⁹	2013	The Netherlands	National Cancer Registry (1999–2009)	189 (ACC only)	DAN centre	Improved 5-year OS (p = 0.047)	
Gratian et al. ⁸	2014	USA	National Cancer Database (1998–2011)	2765 (ACC only)	≥4/year per centre	More radical resection (p<0.001), LN resection (p=0.05) and adjuvant chemo (p<0.011)	
Hauch et al. ²¹	2015	USA	NIS database (2003–2009)	7829 (benign + malign)	>5/year per surgeon	Reduced complications (p<0.05), LOS (p<0.05) and costs (p<0.05)	
Palazzo et al. ²²	2016	UK	Hospital Episode Statistics data (2013–2014)	795 (benign + malign)	≥6/year per surgeon	Reduced LOS and readmissions	No statistical analysis



First author	Year	Country	Data source (years)	Patients (n)	High-volume definition	Main findings for high-volume*	Specific limitations**
Al-Qurayshi et al. ²³	2016	USA	NIS database (2003–2009)	7045 (benign + malign)	≥7/year per surgeon ≥65/year per centre	Surgeons: reduced complications (p<0.001), LOS (p<0.001) and cost (p=0.001) Centres: NS	Hypothetical modeling for cost
Anderson et al. ²⁴	2017	USA	HCUP-NIS (1998–2009)	6712 (benign + malign)	≥6/year per surgeon	Reduced complications (p=0.005), LOS (p=0.003), and cost (p=0.02)	
Lindeman et al. ²⁵	2018	USA	NY Statewide Planning and Research Cooperative System database (2000–2014)	6054 (benign + malign)	>4/year	Reduced in-hospital mortality (p=0.004) and complications (p<0.001)	
Caiazza et al. ²⁶	2019	France	Programme de médicalisation des systèmes d'information database (2012–2017)	9820 (benign + malign)	≥32/year per centre	Reduced 90-day mortality (p=0.01)	90-day mortality after adrenalectomy is generally very low
Stone et al. ²⁷	2021	USA	National Cancer Database (2004–2016)	2886 (malign)	Academic vs. community centres	Improved OS (p<0.05), more radical surgery (p<0.001) with less positive margins (p=0.03), and more chemo (p<0.001)	No definition of threshold
Gray et al. ²⁸	2021	UK	Hospital Episodes Statistics database (GIRFT programme) (2013–2018)	4189 (benign + malign)	≥6/year per surgeon	Reduced readmission with higher volumes, greatest benefit for >20/year (p=0.03)	
Uttinger et al. ²⁹	2023	Germany	Hospital billing data (2009–2017)	17040 (benign + malign)	Volume in tertiles, high volume median 31/year per centre (low volume median 3/year)	Reduced complications (p<0.001), LOS (p<0.001), and in-house mortality (p<0.001; multivar. NS: OR 0.59, p=0.104)	In-house mortality after adrenalectomy is generally very low
Libe et al. ³⁰	2023	France	Cancer registries of FRANCIM (2010–2017)	124 (ACC only)	ENDOCAN-COMETE network centre	Improved 2/3/5-year OS (p=0.025)	Small sample size: only 30% of localized ACC was



First author	Year	Country	Data source (years)	Patients (n)	High-volume definition	Main findings for high-volume*	Specific limitations**
							treated in non-network centre
Rajan et al. ³¹	2024	UK	UKRETS (2004–2021)	4464 (benign + malign)	≥12/year per centre	Reduced complications (p=0.034) and LOS (p<0.001)	Voluntary non-validated registry

ACC: Adrenocortical Carcinoma, DAN: Dutch Adrenal Network, HCUP-NIS: Healthcare Cost and Utilization Project - Nationwide Inpatient Sample, LN: Lymph Node, LOS: Length of Stay, NS: Not Significant, OR: odds ratio, OS: Overall Survival, V: volume.

* Results shown in bold were determined using multivariate analysis.

** General limitations are discussed in section 7 (Discussion and conclusion)

4. Organisation of adrenal cancer care in other countries

4.1 Europe

At the European level, the **European Network for the Study of Adrenal Tumours (ENSAT)**³² was initiated in 2002 to improve the care of adrenal cancer patients. It combines the expertise of three national adrenal networks (COMETE in France, GANIMED in Germany, and NISGAT in Italy) and teams from the United Kingdom. In 2011, ENSAT established its databases, offering the opportunity to register all new patients with an adrenal mass. ENSAT focuses on translational and clinical research, utilising multinational collaboration to accelerate progress in adrenal cancer care.

To achieve this, 'ENSAT Centres of Excellence', interdisciplinary entities within hospitals or research institutes that meet specific certification criteria, were initiated with the following goals:

- Improve research and enrolment of patients in translational and/or clinical trials and pave the way for high-quality and personalised medicine
- Improve structural cooperation among clinical disciplines
- Improve patient follow-up and quality control
- Improve patient documentation and provide data for epidemiology and public health
- Improve recognition and visibility of centres at national and international level
- Provide guidance to establish reference centre standards
- Offer increased networking opportunity

To obtain certification, centres must fulfil several criteria regarding number of patients, medical specialties and structural requirements. The total number of patients (new and follow-up) per year (average of 3 years) seen in the centre is set at ≥ 10 for ACC and ≥ 25 for PPGL.

While the focus of ENSAT is research-driven and specifically for adrenal tumours, the **European Reference Network on Rare Endocrine Conditions (Endo-ERN)**³³ focuses on the clinical practice of a broad range of rare endocrine conditions, including adrenal tumours. Endo-ERN is a network of more than 100 reference centres across Europe. These centres are recognised for their expertise in rare endocrine diseases, fulfilling certain criteria and selected through a rigorous application and evaluation process. By linking patients to these centres, Endo-ERN ensures access to high-quality, expert care..

As ENSAT and Endo-ERN serve complementary roles, centres may hold both designations. ENSAT Centres of Excellences are recognised for outstanding research, registry participation, and clinical expertise in adrenal tumours. Meanwhile, Endo-ERN reference centres are accredited for delivering high-quality, multidisciplinary care for rare endocrine diseases, including adrenal cancers. In addition, several hospitals across Europe are widely regarded as expert centres based on their strong clinical reputation, high patient volumes, and significant research output, even without formal certification. Currently, there is no legal obligation for adrenal tumours to be treated in expert centres. However, referral to such centres is highly recommended due to their specialised expertise and resources.

In addition to the two European initiatives, several individual countries have **national foundations** dedicated to adrenal cancer expertise. These national entities collaborate closely with ENSAT's research infrastructure and Endo-ERN's clinical care framework, collectively contributing to an integrated European system that advances both scientific knowledge and patient outcomes.

Despite existing networks and recommendations, there remains room for improvement. Evidence shows that treatment outcomes for adrenal cancer are better in expert centres.^{31,34} Nevertheless, many patients in Europe continue to receive care in low-volume hospitals without expertise.^{22,29,35} This highlights the need for a formal legal framework that clearly defines what constitutes an expert centre, including minimum case volumes, multidisciplinary collaboration, and quality standards, and mandates referral to such centres as a structural part of healthcare delivery.

4.2 France

The French National Institute of Cancer, supported by the Ministry of Health, initiated a national network 'ENDOCAN-COMETE' in 2009 to organise care and research for patients with ACC and PPGLs.³⁶

The ENDOCAN-COMETE network includes:

- a tri-site coordinating centre
- 8 regional expert centres
- 23 associated centres
- a national network of expertise for the anatomopathological diagnosis of ACC and PPGLs in adults (COMETEmath)
- an associated research network (COMETE-Bio)

The missions of the ENDOCAN-COMETE network are:

1. Expert mission: double reading of tumour samples, referral national multidisciplinary staff
2. Care practice and equity safeguarding mission: drafting and/or updating national best practice guidelines
3. Reference mission: patient access to medical teams, technical platforms or highly specialised or innovative treatments (proton therapy, immunotherapy, etc.)
4. Observation mission: exhaustive registration of cases in an interoperable clinical-national database (French Network of Cancer Registries FRANCIM)
5. Mission of contribution to research: translational research, clinical research, publications
6. Mission of training health professionals
7. Patient information mission, role of patient associations
8. Structuring and coordination mission
9. Monitoring mission of this specific organisation

While the network doesn't publicly specify a numerical threshold like a minimum number of adrenalectomies per year, it does emphasize centralisation of care and expertise in adrenal tumours. Referral of ACC/PPGLs patients to ENDOCAN-COMETE expert centres is recommended by national guidelines and policy, but is not legally mandatory. An evaluation after 10 years of activity showed that the coverage rate of new patients discussed in a referral national multidisciplinary staff over the estimated number was 68%. There was an 84% concordance between the treatment proposed in the multidisciplinary staff and the treatment administered. They concluded that through the establishment of the ENDOCAN-COMETE network, France has achieved a harmonised clinical approach to managing ACC/PPGLs.³⁷ In addition, a retrospective cohort study showed that the survival of patients with localized ACC significantly improved when treated at a network centre compared to a non-network centre.³⁰ More detailed study information can be found in the table in section 3.4.

4.3 Germany

Founded in the late 1990s already, GANIMED (German Adrenal Network for Improving Medical research and Education) was a pioneering national initiative in Germany focused on adrenal cancer research and clinical care. It developed a national ACC registry, and supported collaboration between medical specialists across Germany to standardise care for adrenal cancer. Following its contribution to the founding of ENSAT in 2002, GANIMED no longer exists as a standalone entity. However, its influence persists through ENSAT, the leadership of German institutions such as University Hospital Würzburg, and the continued use of the German ACC registry.

A large retrospective study, analysing 17.040 adrenalectomies performed in Germany between 2009 and 2017, showed a highly variable caseload among German hospitals. Low volume hospitals (median of 3 patients per year) accounted for 85% of the hospitals analysed, and these performed an equal number of adrenalectomies as the 2.8% of hospitals in the high-volume category (median of 31 patients per year). Moreover, the low volume hospitals seem to treat the most complex cases, with a higher proportion of malignant adrenal tumours compared to high-volume hospitals (36.1% versus 26.4%, $p < 0.001$). These numbers are concerning, as the study, along with other studies, showed a clear volume-outcome relationship for adrenalectomies. Therefore, the authors advocate for the referral of adrenal cancer patients to experienced high-volume centres for surgery.²⁹

4.4 Italy

NISGAT (National Italian Study Group on Adrenal Tumours) was formed in 1998 and initially included several university centres across Italy working together on adrenal cancer research and clinical coordination. In 2002, it became part of ENSAT, whereafter it no longer functioned independently but had been fully integrated into ENSAT's ongoing European coordination framework.

A recent nationwide survey investigated current practices in adrenal surgery across Italy, gathering responses from 248 surgeons. Despite strong evidence supporting a volume-outcome effect for adrenalectomies, the survey revealed that patients with adrenal disease are often treated in low-volume hospitals, by surgeons performing fewer than 10 adrenalectomies per year.³⁵ These findings underscore the urgent need for a global consensus on the minimum thresholds that define high-volume surgeons and centres.

4.5 United Kingdom

The UK follows European guidelines (e.g. from ENSAT) for diagnosis and treatment, but there is no formal national registry or mandatory referral system for adrenal cancer. Recognising these gaps in care and data, the National Health Service England recently published a national report advocating for centralisation of adrenal cancer care in the UK.³⁸ They advise a minimum of 6 adrenalectomies per surgeon per year and a minimum of 20 if they are operating on patients with adrenal cancer and pheochromocytoma. In addition, a national registry for adrenal cancer is being developed by the Society for Endocrinology and AMEND (a patient support group). Moreover, a major UK-wide observational study, the National Study of Adrenal Tumours (NCT06870396), is currently open for recruitment. The aim of this study is to answer questions about survival by gathering data, hoping as such to improve understanding and treatment of adrenal cancer.³⁹

Analysis of the Hospital Episode Statistics data of 2013-2014 revealed that only 13% of adrenal surgeons performed a minimum of 6 adrenalectomies per year. Moreover, 84% carried out a median of just 1 annually.²² In line with this, a subsequent analysis covering the period 2013-2018 showed that only one third of surgeons met the recommended minimum of 6 adrenalectomies per year, as advised by European guidelines.^{28,40} Considering the volume-outcome relationship in adrenal surgery, such low procedural volumes raise concerns regarding the quality of care, and may not align with optimal patient outcomes.²⁸

In awaiting of the national adrenal cancer registry, a large retrospective cohort study used data from UKRETS to investigate the impact of adrenal surgeon volume on outcome. UKRETS is a national database of endocrine surgery, with voluntary registration. Between 2004 and 2021, a total of 4464 patients undergoing an adrenalectomy were analysed. The results showed a significantly lower complication rate for surgeons doing a minimum of 12 operations per year ($p=0.034$) and 20 per year ($p<0.001$). These findings support the centralisation of care for adrenal cancer to expert surgeons performing minimal 12 adrenalectomies per year.³¹

4.6 The Netherlands

The Dutch Adrenal Network (DAN)/Bijniernetwerk Nederland (BNN), established in 2004, brings together eight university hospitals and the Máxima Medical Centre in a coordinated effort to improve and formalise care for patients with adrenal disease, primarily ACC.^{9,10} These centres meet the criteria defined in the policy framework 'Expert Centres for Rare Diseases 2025', issued by the Ministry of Health.^{41,42} Notably, these criteria do not specify a precise minimum threshold for the number of cases.⁴² In 2007, the DAN registry was set up, including data of Dutch patients with ACC since 1965.¹⁰ In addition, since 2019, the Netherlands Cancer Registry (NCR) has expanded its data collection for patients with ACC to include tumour-specific characteristics such as hormone production.

However, since care for adrenal cancer is not formally centralised in the Netherlands, treatment for ACC is not exclusively confined to DAN hospitals. Despite this, a retrospective analysis based on data from the Netherlands Cancer Registry (2014 - 2015), showed that most ACC treatments occurred within a DAN centre; 87.2% of surgeries (compared to 56.4% between 1999 and 2009) and 94.5% of medical treatments.⁴³ Further increasing patient referrals to DAN centres is strongly recommended, particularly for surgery, as studies have shown that surgery for ACC performed within DAN centres leads to improved patient outcomes such as significantly better OS.^{9,10}



5. International recommendations/guidelines and consensus statements

1. European Society of Endocrinology (ESE) clinical practice guidelines on the management of adrenal incidentalomas, in collaboration with the **European Network for the Study of Adrenal Tumors (ENSAT)** (Fassnacht, 2023)³

- a. It is recommended that patients with adrenal incidentalomas are discussed in a multidisciplinary expert team meeting if malignancy is suspected and/or adrenal surgery is considered.
- b. It is suggested that minimally invasive adrenalectomy is performed by an expert high-volume adrenal surgeon (no volume threshold mentioned).
- c. It is recommended that open adrenalectomy is performed by an expert high-volume adrenal surgeon (no volume threshold mentioned).

2. Adrenocortical carcinomas and malignant pheochromocytomas: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up (Fassnacht, 2020)²

- All patients with suspected and proven ACC or PPGL should be discussed in a multidisciplinary expert team meeting, at least at the time of initial diagnosis (ideally before surgery) and in case of progressive disease.
- Adrenal surgery should be carried out only by surgeons with appropriate expertise and experience. The lack of consensus on what is defined as appropriate experience and the absence of evidence that a specific experience in adrenal surgery translates into improved outcomes limit any recommendations concerning this issue. In addition to expertise in adrenal surgery, sufficient experience in oncological surgery is essential. For best clinical outcome, the entire operative team (including anaesthesiologists) should be well-trained in adrenal surgery.

3. European Society of Endocrine Surgeons (ESES): Volume-outcome correlation in adrenal surgery—an ESES consensus statement (Mihai et al. 2019)⁷

- Adrenal surgery should be performed only in centres doing ≥ 6 cases/year.
 - For ACC the threshold is ≥ 12 adrenal operations/year.
- All such centres should have an integrated multidisciplinary team.
- Surgeons should contribute data to EUROCRINE and ENSAT registries.

4. European Society of Endocrinology (ESE) Clinical Practice Guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the **European Network for the Study of Adrenal Tumors (ENSAT)** (Fassnacht, 2018)⁴⁰

- It is recommended that adrenal surgery for suspected/ confirmed ACC should be performed only by surgeons experienced in adrenal and oncological surgery.
- A minimal annual workload of 6 adrenalectomies/ year is required to ensure sufficient experience in adrenal surgery, but >20 adrenalectomies/year are desirable for those involved in surgery for ACC.

6. Extra reading material

6.1 Reports from Belgium

1. Cancers of the endocrine organs – endocrine neoplasms: Preferred model of care and criteria for reference centres - KCE Report 219 Addendum (2014)⁴⁴

The KCE (Belgian Health Care Knowledge Centre) suggests that the entire care pathway, from diagnosis to follow-up, of patients with suspected and/or diagnosed adrenal cancer should take place exclusively in reference centres. The report outlines both general and specific criteria for the designation of reference centres, including requirements related to (para-)medical staff, infrastructure and MOC. Regarding the minimum patient volume, it notes that, given the rarity of the disease, a fixed threshold cannot be defined. They suggest determining such a threshold after a five-year observation period, based on the actual number of cases treated in the reference centres.

2. Referentiecentra voor zeldzame en complexe kankers - KOTK (2020 and 2023)^{45,46}

In 2020, KOTK (Kom op Tegen Kanker) published a dossier explaining the rationale and criteria for establishing reference centres. These proposals were inspired by many interviews and meetings with healthcare providers, patient representatives and policy makers. Based on this dossier, KOTK formulated ten specific policy recommendations in 2023 aimed at improving care for patients with rare and complex cancers through the development of dedicated reference centres. ACC is mentioned as one of these rare cancers of the endocrine organs.

6.2 Other treatment modalities

1. Mitotane

Adjuvant mitotane therapy is recommended for patients with ACC who are at high risk of recurrence. Achieving therapeutic plasma levels has been associated with improved outcomes, but this requires specialised monitoring and clinical expertise, which is more likely present in high-volume centres. No definitive volume–outcome relationship has been established for mitotane administration. However, a narrative review of 2024, including relevant studies about mitotane, suggests that specialised centres may be better equipped to achieve therapeutic levels and manage treatment effectively.⁴⁷ In line with this, Fassnacht et al. recommend that patients receiving mitotane therapy be supervised in centres managing at least 10, and preferably 20, such patients annually.⁴⁸

2. Radiotherapy

Radiotherapy may be indicated in patients with ACC after incomplete resection. While robust evidence for a clear volume–outcome relationship is lacking, delivery within a dedicated endocrine oncology program is recommended.⁴⁹

7. Discussion and conclusion

Because of its rarity and complexity, the treatment of adrenal cancer requires a high level of expertise. A substantial body of research suggests that higher surgical volume, at both the surgeon and hospital levels, is associated with improved outcomes in adrenal cancer treatment. While all studies identified a volume–outcome relationship, its strength varied. In particular, two studies observed better outcomes in univariate analyses, but this did not reach significance in multivariate analyses (see Table in section 3.4 for details).^{15,29} However, since both studies mainly included adrenalectomies for benign conditions (Murphy et al. 83%, Uttinger et al. 69%) and only included in-hospital endpoints (no longer-term follow-up), extrapolating their results to adrenal cancer should be done cautiously. Moreover, the Murphy study excluded patients with an additional kidney removal (thus excluding part of the adrenal cancer patients) and mentioned an underestimation of measured in-hospital complications. Therefore these studies are less relevant for the adrenal cancer population.

Overall, the results from this literature study underscore the importance of centralising adrenal cancer surgeries to high-volume centres and/or surgeons to optimise patient care. To note, volume–outcome studies for adrenal cancer have only been conducted for surgery, which is unsurprising as it is the primary treatment. For other modalities, such as mitotane and radiotherapy, there is no direct evidence linking treatment volume to patient outcomes. However, few studies report that tertiary referral centres show increased adjuvant therapy use.^{8,11,27}

Although notable evidence supports a relationship between adrenalectomy volume and patient outcomes, several important considerations must be addressed:

1. The available research is based on retrospective studies using databases from registries, hospital billing records, or surveys. These sources mainly contain administrative data, which often lacks relevant clinical details. In addition, coding errors and selection bias are common issues. Furthermore, readmissions are often not included in these databases, resulting in underestimation of complication rates and mortality.
2. The definition of ‘high-volume’ greatly varies between studies. Some evaluate the number of operated patients per surgeon, while others use the centre’s number. Surgeon volume reflects individual technical expertise, whereas centre volume encompasses the entire (para-)medical team, institutional infrastructure and organised care pathways. Of course, both are inherently interconnected, and optimal centralisation involves performing adrenalectomies in high-volume centres by experienced surgeons.³⁴ Furthermore, the threshold for defining ‘high-volume’ is still under debate and differs across studies. The ESES consensus statement of 2019 recommends that adrenal surgery should be performed only in centres doing minimal

6 cases per year, with a minimum of 12 cases annually for ACC.⁷ The ESES/ENSAT guidelines of 2018 further advise that adrenalectomy should only be conducted by surgeons performing at least 6 procedures per year as a general minimum, and 20 procedures per year for ACC.⁴⁰ The latter are supported by large-scale studies using data from the UKRETS and GIRFT databases.^{28,31} Nonetheless, a universally accepted evidence-based threshold, validated through robust research, is still required to substantiate the rationale for centralising adrenal surgery.

3. Most available studies address adrenalectomy in the context of general adrenal pathology, rather than focusing specifically on adrenal cancer. This broad approach may overlook the distinct clinical and perioperative challenges associated with malignant adrenal tumours. Although the surgical technique may be similar, these cases often demand higher levels of expertise, multidisciplinary coordination, and risk management. As a result, volume-outcome thresholds derived from pooled data may underestimate the complexity of cancer surgery. Indeed, while overall adrenalectomy volume is associated with better surgical safety and technical surgical expertise (complication rates, shorter hospital stays, better perioperative outcomes), specific adrenal cancer volume is associated with better cancer outcomes and optimal cancer management (R0 resection, recurrence, survival) as well as performing more appropriate lymph-node dissections. However, since most centres treat very few adrenal cancer patients, resulting in too few cases for statistical analysis, overall adrenal surgical volume is often used as a proxy. Stratifying outcomes by indication allows for more tailored recommendations and better reflect the needs of high-risk patients. Moreover, ACC and PPGL surgeries warrant prioritisation in centralisation strategies over adrenalectomies for benign pathologies. Nevertheless, it should be noted that adrenal cancer is not always identifiable preoperatively, as many malignant tumours initially present as incidentalomas. However, thorough preoperative evaluation remains essential, particularly to assess for hormonal excess, which may significantly impact perioperative risk and management. Functional workup, imaging characteristics, and multidisciplinary review help guide surgical planning and determine urgency and approach. Even when malignancy is not confirmed until after adrenalectomy, early identification of functional or radiologically suspicious lesions can improve outcomes and reduce complications.^{2,3}
4. In the context of adrenal cancer treatment, the observed trend towards improved outcomes in high-volume centres likely reflects more than just surgical expertise. These centres typically organise multidisciplinary case discussions, combining the expertise of surgeons, oncologists, radiotherapists, endocrinologists and radiologists. This collaborative approach is further strengthened by adherence to up-to-date guidelines and possibility of participation in clinical trials.

Most studies indicate that adrenalectomy performed by high-volume surgeons or at high-volume centres is associated with reduced postoperative complications, lower mortality rates, and shorter hospital stays. A subset of these studies also reports improved overall survival. In terms of surgical technique, procedures conducted in these settings tend to be more radical, characterised by a higher frequency of R0 resections and more consistent performance of lymphadenectomy.

Across Europe, collaborative initiatives such as ENSAT and Endo-ERN have laid the base for integrated research and clinical excellence, while national networks in France, Germany, Italy, the UK, and the Netherlands have made strides toward centralisation. However, despite the evidence supporting volume-outcome relationships, many patients are still treated in low-volume settings. To ensure general access to high-quality care, a formalised framework defining expert centres and mandating referral pathways is recommended. In line with this, various European guidelines consistently emphasise that adrenal tumour management should occur in high-volume centres with multidisciplinary expertise, particularly for malignant cases. Surgery should be performed by experienced adrenal and oncological surgeons, with minimum annual case thresholds to ensure quality. However, definitions of surgical expertise remain vague, and implementation across Europe is inconsistent.

To summarise, adrenal cancer treatment requires specialised expertise, and evidence suggests that surgeries performed by high-volume surgeons or in high-volume centres lead to better outcomes. While most data focus on adrenalectomy, centralisation also promotes multidisciplinary care and access to clinical trials, which may further improve patient management.



8. Abbreviations

ACC	Adrenocortical Carcinoma
DAN	Dutch Adrenal Network
Endo-ERN	European Reference Network on Rare Endocrine Conditions
ENSAT	European Network for the Study of Adrenal Tumors
ESE	European Society of Endocrinology
ESES	European Society of Endocrine Surgeons
GANIMED	German Adrenal Network for Improving Medical research and Education
HCUP-NIS	Healthcare Cost and Utilization Project - Nationwide Inpatient Sample
KCE	Belgian Health Care Knowledge Centre
KOTK	Kom op Tegen Kanker
LN	Lymph Node
LOS	Length Of Stay
NCR	the Netherlands Cancer Registry
NISGAT	National Italian Study Group on Adrenal Tumours
NS	Not Significant
OS	Overall Survival
PPGLs	Pheochromocytomas and Paragangliomas

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