Adaptive ROC analysis in Carotid Atherosclerosis Diagnosis for Endarterectomy

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Abstract

Atherosclerosis disease of the carotid is one of the major reasons for stroke and a leading cause for morbidity and mortality. An accurate diagnosis and severity quantification of the disease is therefore needed to prevent symptoms and decide the appropriate treatment. The most important indicator for the risk of symptoms is the Degree of Stenosis (DS). Very recently, a new score was proposed, called Enhanced Activity Index (EAI), which is more complex but more accurate than DS. EAI, however, only takes into account medical information about the patient.

In this work, other factors besides the medical ones, e.g., age, gender, expected costs and effects of surgery to the patient, are considered together with EAI in order to improve the information available for the decision making process of endarterectomy. Quality-Adjusted Life Years (QALY), and its respective Incremental Cost-Effectiveness Ratio (ICER), when compared to medical therapy, will be considered.

The optimal EAI cut-off for endarterectomy is computed under the Receiver Operating Characteristics (ROC) framework. A Graphical User Interface (GUI) is described to help the medical staff in the decision making process. The optimal decision point is adjusted according to population characteristics, inherent to the ROC curve, patient information and economic aspects.

The method is tested with real data acquired at Instituto Cardiovascular de Lisboa and Department of Vascular Surgery, Hospital de Santa Maria, Lisbon. The created tool outputs coincident results to the ones presented in different studies of the bibliography. This preliminary approach to the problem lead to promising results that strongly suggest its application at medical facilities in clinical practice. Nevertheless, it would be interesting to incorporate both the EAI and the economical information in a global index.

Keywords

Atherosclerosis, Carotid Endarterectomy, Receiver Operating Characteristic curve analysis, Enhanced Activity Index, Quality-Adjusted Life Years

Resumo

A doença aterosclerótica da carótida é uma das principais razões para a ocorrência de Acidentes Vasculares Cerebrais e uma das principais causas de morbidade e mortalidade. Um diagnóstico preciso e quantificação da gravidade da doença são, portanto, necessários para prevenir o agravamento da doença e decidir o tratamento adequado. O indicador mais importante para o risco de agravamento da doença é o grau de estenose (DS). Muito recentemente, um novo indicador foi proposto, denominado Enhanced Activity Index (EAI) que, apesar de mais complexo, é mais preciso do que o DS. O EAI, no entanto, só tem em conta informações médicas sobre o paciente.

Neste trabalho, são considerados a idade, sexo, custos esperados e efeitos da cirurgia no paciente, juntamente com o EAI, com o intuito de melhorar a informação disponível para a tomada de decisão da endarterectomia. Valores para os anos de vida ajustados pela qualidade (QALY) e respectiva relação incremental custo-efetividade (ICER) serão considerados.

É apresentada a interface gráfica (GUI) desenvolvida para ajudar a equipe médica, onde o ponto de decisão é ajustado de acordo com as características da população, inerentes á curva ROC, as informações do paciente e aspectos económicos.

O método foi testado com dados reais adquiridos no Instituto Cardiovascular de Lisboa e no Departamento de Cirurgia Vascular do Hospital de Santa Maria, em Lisboa. A ferramenta criada gera resultados coincidentes com diferentes estudos da bibliografia. Esta abordagem preliminar do problema levou a resultados promissores que sugerem a sua aplicação na prática clínica. No entanto, seria interessante incorporar tanto o EAI como a informação económica em conjunto num índice global.

Palavras Chave

Aterosclerose, Endarterectomia, Curvas ROC, Análises, Anos de vida ajustados pela qualidade.

Contents

List of Figures

List of Tables

Abbreviations

ACST Asymptomatic Carotid Surgery Trial

AI Activity Index

AUC Area Under the Curve

CAD Computer Aided Diagnosis

CAS Carotid Artery Stenting

CBA Cost-benefit Analysis

CEA Carotid Endarterectomy

CE Analysis Cost-effectiveness Analysis

CUA Cost-utility Analysis

CT Computed Tomography

DDIC Descending Diagonal Intersection Criterion

DS Degree of Stenosis

EAI Enhanced Activity Index

FN False Negative

FP False Positive

FPR False Positive Rate

GUI Graphical User Interface

ICER Incremental Cost-Effectiveness Ratio

ICVL Instituto Cardiovascular de Lisboa

LOS Length of Stay

MI Myocardial Infarction

NASCET North American Symptomatic Carotid Endarterectomy Trial

NICE National Institute for Health and Clinical Excellence

QALY Quality-adjusted life-years

ROC Receiver Operating Characteristics

RCT Randomized Control Trials

TIA Transient Ischemic Attack

TN True Negative

TP True Positive

TPR True Positive Rate

1

Introduction

Contents

The atherosclerotic disease, which is the main cause of stroke, is one of the main causes of morbidity and mortality in developed countries like Portugal. Stroke is regarded as the first cause of morbidity and continued incapacity in Europe and is also the second most common cause of dementia. It is also responsible for temporary and permanent disabilities with strong socio-economic impact.

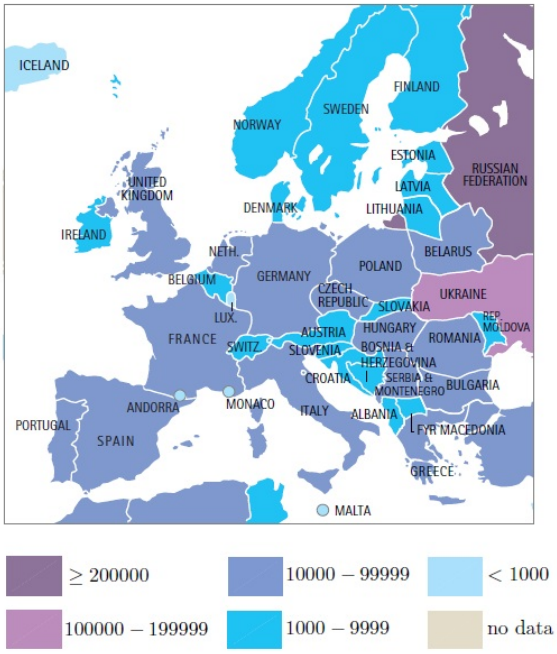


Figure 1.1: Distribution of deaths from stroke in Europe.

The correct indication of treatment to a patient is crucial, in order to obtain the best possible results in the recovery of the patient. Endarterectomy is one alternative of surgical treatment to remove the atherosclerotic plaque that, despite the great results in terms of health recovery, has an associated risk to the patient. Also, it is considered an expensive alternative of treatment when compared to medical therapy. Hence, an accurate evaluation of the need for this intervention is critical to save the patient's life, when it is needed, and at the same time to avoid its use when it is not absolutely necessary, subtracting the patient to the risk of surgery and reduce unnecessary costs.

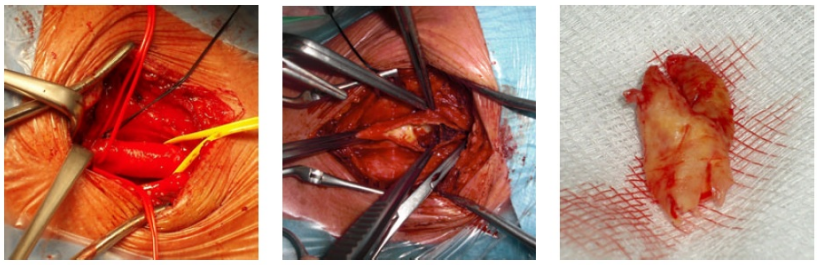


Figure 1.2: Photos taken during CEA, showing carotid bifurcation (left), thrombus (center) and excised plaque (right) [2].

Previous work presented the Enhanced Activity Index (EAI), calculated threw a software tool to aid diagnosis using clinical data and ultrasound images of the carotid artery of the patient to assess

the state board and calculate an indicator of instability or danger, and therefore the risk of stroke. This indicator is however only medical and does not account for the economic factors of the decision to submit a patient to endarterectomy. Moreover, it provides no notion about life expectancy to the patient after surgery or associated incremental quality of life.

This work aimed at developing a software tool to assess clinical decision support to the physician that provides an advanced Receiver Operating Characteristics (ROC) analysis, estimates of expected costs and effects for the patient in various scenarios. The results are presented in terms of Life Expectancy, Quality-adjusted life-years (QALY) and Incremental Cost-Effectiveness Ratio (ICER). The referred indicators and ROC analysis (that provides an optimal cut-off point for the decision) should be analysed together with the objective risk of stroke, obtained by the EAI, developed by Instituto Superior Técnico and the Faculdade de Medicina da Universidade de Lisboa. This information will assist the decision making process of indicating a patient to endarterectomy, as the adequate treatment for carotid atherosclerosis.

In this thesis we start to explain the background of the problem and the context about atherosclerosis and treatment possibilities. Chapter 2 also addresses the use of ROC analysis as a tool used in clinical decision support and introduces the economic evaluation theme, to understand basic concepts and the types of economic evaluation existent. Chapter 3 represents a literature review of ROC analysis and economic analysis of endarterectomy. Subsequently, a methodology is proposed in Chapter 4 where an advanced ROC analysis is suggested, based in criteria for best operating point selection. Economic analysis presented before allow to collect utility values for each health state of a carotid atherosclerosis patient. In Chapter 5, a tool developed in the software Matlab is presented. Finally in Chapter 6, results are showed using the outputs of the tool created and, in Chapter 7, some conclusions are gathered allowing a perspective of future work possibilities.

1.1 Previous contributions

This thesis was developed based on the work presented by José Seabra [2]. It is also worth mentioning that two articles were submitted and accepted for the Pattern Recognition Conferences (RecPad) in 2011 and 2012 [3], [4]. These can be consulted in Appendix B.

2

Context

Contents

This chapter aims to present information about the Atherosclerotic disease and associated risk of stroke. Endarterectomy is the intervention for atherosclerotic plaque removal in the carotid arteries and it is referred as one of the most used surgical procedures in the prevention of neurological complications. The use of an index to understand the complexity of the stenosis introduced the degree of stenosis. It is important to understand the role of Enhanced Activity Index as a more complete diagnostic index that allows wider and thorough plaque classification, leading consequently to improved prevention of neurological complications. ROC curves are an important tool in clinical medicine to help in the medical decision process. They are of most relevance when different diagnostic scenarios are analysed, allowing to understand which one has better diagnostic strength. It is then presented the basics of economic analysis, as complementary information for a more aware decision process.

2.1 Atherosclerosis

2.1.1 Historical Perspective

Atherosclerosis is a disease that has followed mankind since its early beginning. A recent study proves that humans in ancient times had the genetic predisposition and environment to promote the development of atherosclerosis [5]. This study has Computed Tomography (CT) images that corroborate exactly the existence of calcification of arteries, like the aortic or femoral arteries.

In 1904, Felix Marchand introduced the term atherosclerosis and suggested that atherosclerosis was responsible for nearly all obstructive processes in the arteries [6]. In the **19th** century, there were two major contributions for the research in the pathogenesis of atherosclerosis. These contributions, from Carl von Rokitansky [7] and Rudolf Virchow [8], described cellular inflammatory changes in atherosclerotic vessel walls. They are, none the less, different approaches, as von Rokitansky suggested blood as being the basis of all vital processes with his humoral theory and Virchow highlighted the important role of inflammatory arterial changes for the pathogenesis of the atherosclerotic disease [9]. Then, several studies were revealed along the **nineteenth century**. In 1910, Adolf Windaus showed that atheromatous lesions contained 6 times as much free cholesterol and 20 times as much esterified cholesterol as a normal arterial wall [10]. Using cholesterol-fed rabbits to produce experimental atherosclerosis, Nikolai Anichkov and S. Chalatov demonstrated, in 1913, that cholesterol, alone, that caused these atherosclerotic changes in the rabbit *intima* [11].

It is important to understand that all the referred investigations were taken forward by the correct understanding of the consequences of atherosclerosis. In the beginning of the 20th century, two names are associated to evidences that carotid partial obstruction could be responsible for neurological symptoms as a result of thromboembolism or fragments of atheromatous plaques, Hans Chiari [12] and Ramsey Hunt [13]. Egas Moniz also had an important role, in the diagnose of atherosclerosis, with the discovery of cerebral angiography in 1927 [14]. His work on occlusive cerebrovascular disease provided, in 1937, the original description of internal carotid occlusion documented by angiography [15]. The association of carotid artery disease and stroke was still weak, as further investigation, by C. Miller Fisher [16], only in 1951, was the turning point for this matter. Fisher reported the clinical

implications of transient ischemic attacks and their relationship to carotid artery disease and stroke.

2.1.2 Atherosclerotic disease and associated risk of stroke

Atherosclerosis is a progressive disease characterized by the formation in the walls of large, and medium, sized arteries of lesions called atherosclerotic plaques [17]. It is an epidemiological reality for the XXI century, with no apparent genetic susceptibility, but results from unhealthy lifestyles. Some risk factors associated with atherosclerosis are obesity, diet, diabetes, hypertension, blood cholesterol concentration and smoking. The risk is even higher if more than one of the referred factors are combined. These factors can be divided in two categories: Nonmodifiable and Potentially controllable. Examples for the former are obesity, increasing age and physical inactivity; the latter consist of hypertension, diabetes and unsaturated fat intake, for example. The one essential underlying cause of serious atherosclerosis seems to be a high concentration of low density lipoprotein in the blood, which reflects a high intake of the referred dietary saturated fat [18]. Nevertheless, atherosclerotic plaque is present in 50% of individuals aged 20 to 29 years, rising to 80% in individuals aged 30 to 39 [19], which indicates that age is also significant.

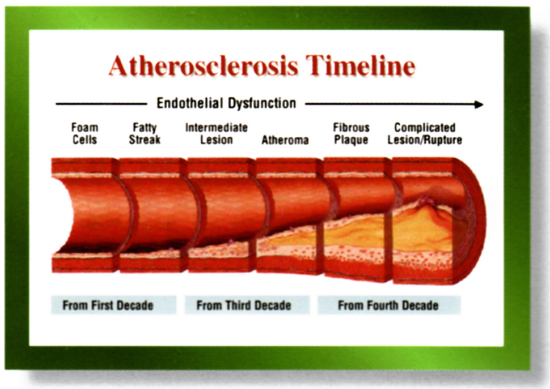


Figure 2.1: Representation of atherosclerosis time line [20].

For its systemic characteristic, symptomatic atherosclerotic disease most often involves the arteries supplying the heart, kidneys, lower extremities and the brain [21]. Consequently, the major consequences of arterial atherosclerosis are myocardial infarction, aortic aneurisms, peripheral vascular disease and cerebral infarction (stroke). Stroke is one of the leading health problems in the United States today, with 600 000 new or recurrent strokes occurring annually. Stroke is the third leading cause of death and the principal cause of long-term disability [22].

Since early ages lipid streaks begin to appear in the aortic intima [18]. They are formed of accumulated lipids (mostly low-density lipoproteins) and circulating monocytes, that cross the endothelium, enter the *intima* of the vessel wall and differentiate to become macrophages [23], which have a foam like appearance and aggregate on the blood vessel. With time, the fatty streaks grow larger, forming larger plaques by smooth muscle tissue and surrounding fibrous proliferation [23]. Hence, lower blood flow and the possibility of the plaques to have fissure and haemorrhages, which in turn may

lead to thrombosis (particularly in the carotid arteries) embolization and consequent ischaemia [18] are possible complications. Atherosclerosis accounts for the great majority of thrombosis in the internal carotid arteries. Severe atherosclerosis is seen in the carotid sinus, more frequently than in any other site, and ulceration, calcification and hemorrhage into atheromatous plaques are common in this situation [24]. Rose, G., refers as treatment for arterial disease thrombolytic drugs, control of hypertension, blood sugar and lipids, and also surgical procedures [18]. Surgical interventions are only advised if the neurological and cardiac morbidity, together with the mortality associated with the procedure, are significantly lower than what one expects from the medical treatment alone [25].

For the case of carotid atherosclerosis, it is represented in Figure 2.2 the steps in the diagnosis and treatment workflow for a carotid atherosclerosis patient. Considering that a patient can resort a health service when coming from the decision of primary or private health providers, a specialty consultation is performed to better assess the health state of the patient. Also, a patient can arrive at the emergency health services because of a symptomatic situation. It is defined a diagnosis strategy where imaging tests are performed, as well as, other laboratory tests needed. Ultrasound imaging has become a standard procedure for medical diagnosis worldwide and treatment options for carotid artery disease will depend on the severity of stenosis (narrowing) of the artery, whether the patient is symptomatic or asymptomatic and general health or other conditions affecting the patient [2]. Eco-Doppler enables, from the morphological point of view, the quantification of carotid stenosis by the measurement of the longitudinal cut, which compares the minimum luminal diameter with the carotid bulb diameter (European method) or with the distal intern carotid (American method) [26]. According to the diagnosis result, if the patient does not have atherosclerosis, no further action is needed, despite a re-evaluation consult in 2 to 5 years. When a patient is diagnosed with stenosis, it can be divided into mild, moderate, severe and quasi-occlusive stenosis. With this information, the physician can decide wether to perform medical therapy, based on antiplatelet therapy, antihypertensive treatment and lipid-lowering therapy [27], or surgery. For both options mentioned, the patient will need to be re-evaluated every 6 months to assess the condition of the disease.

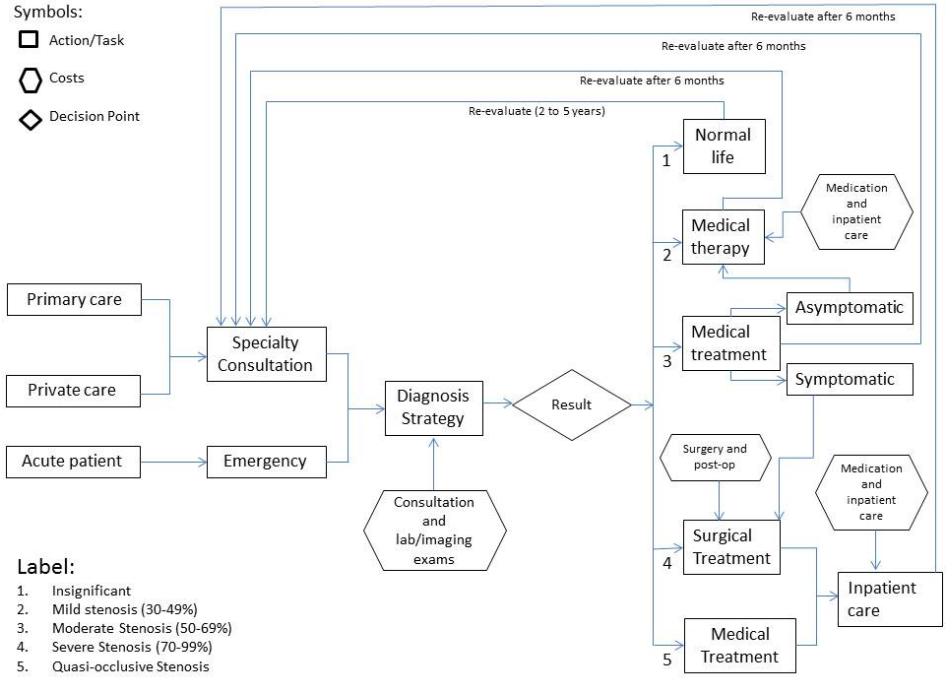


Figure 2.2: Workflow enhancing the possible outcomes for carotid atherosclerosis diagnosis.

Despite the Asymptomatic Carotid Atherosclerosis Study [28] referring that patients with asymptomatic carotid stenosis of 60% or greater reduction in diameter and whose general health makes them good candidates for elective surgery will have a reduced 5-year risk of ipsilateral stroke, a meta-analysis of individual patients data from the European Carotid Surgery Trial (ECST) [29] and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [30], showed that surgery was harmful in patients with less than 30% stenosis, of no benefit in those with 30 to 49% stenosis, of some benefit for 50 to 69% stenosis, and highly beneficial for those with 70% or more stenosis without near-occlusion [31]. A typical symptomatic NASCET patient is a patient within 120 days from the last symptomatic event. Carotid endarterectomy is indicated for most patients with a recent non-disabling carotid-territory ischaemic event when the symptomatic stenosis is greater than about 80%. Both studies also concluded that a very small benefit arises from surgery to patients with quasi-occlusive stenosis, as these patients had a paradox low risk of stroke under medical therapy, probably because of effective collateral circulation [32]. Moreover, the classification of moderate stenosis is worthy of a thorough observation of patient condition, due to surgery associated risk and other aspects. The presented division that asymptomatic patients would benefit of medical therapy, whereas symptomatic patients would benefit from a surgical intervention is not always applicable. For example, female patients do not benefit of endarterectomy when they have symptomatic 50-69% stenosis, for their lower ipsilateral risk of stroke when compared to men [28]. For the aforementioned, Figure 2.2 does not represent a fixed approach for the diagnosis and treatment of carotid atherosclerosis. Medical therapy has changed dramatically since the 1980's, where the anti-platelet therapy used consisted in aspirin, which led to a drop in the annual rates of stroke for asymptomatic carotid stenosis patients from 2.5% to less than 1% [33].

2.2 Treatments for carotid atherosclerosis

Stroke is the third leading cause of death in the United States, after heart disease and cancer, and a leading cause of disability [34]. There are several factors that must be evaluated for the selection of treatment for the carotid disease. Among these are stenosis severity of the artery and consequent narrowing, as shown in Figure 2.3, whether the patient is symptomatic or asymptomatic and general health or other conditions affecting the patient. Symptomatic disease in the carotid circulation encompasses a spectrum of presentations from transient ischemic attacks to embolic or thrombotic stroke and, at times, is paradoxical in that the degree of collateral circulation may allow severe carotid lesions to present with only minimal symptoms [35]. Any consideration of surgery for symptomatic carotid disease must be based on objective comparison of surgical morbidity and results with both the natural history of the disease process and the best available medical therapy [35]. Asymptomatic severe carotid stenosis is generally accepted to refer to atherosclerotic narrowing of the proximal internal carotid artery exceeding approximately 50% to 60% diameter reduction in the absence of symptoms of ipsilateral stroke or Transient Ischemic Attack (TIA) [36]. The mentioned risk factors must be controlled, like arterial blood pressure, recommendation for smoking cessation, regular and appropriated physical exercise, dietetic control [37]. Medical treatment can also include platelet aggregation inhibitors (acetylsalicylic acid or other agents).

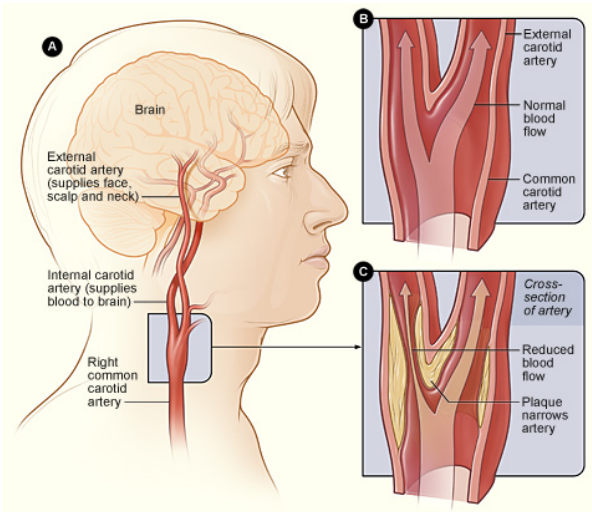


Figure 2.3: In the left is shown the location of the right carotid artery in the head and neck. In the center is a cross-section of a normal carotid artery that has normal blood flow. On the right is shown a carotid artery that has plaque buildup and reduced blood flow.

There are clinical studies suggesting that patients with mild coronary artery disease (less than 50% stenosis) may be at relatively high risk of developing clinical events, that the angiographic degree of stenosis is a poor predictor of subsequent culprit lesions and that angiography cannot differentiate stable from unstable lesions with a substantial degree of confidence [19].

There are surgical alternatives to medical treatment that represent specific intervention for carotid artery disease. It is of most importance the correct plaque classification, in order to select the best treatment alternative for a patient. The NASCET [30] and ECST [29] studies developed in the late 90's

allowed a objective analysis of the advantages and disadvantages of endarterectomy in the carotid atherosclerosis disease. They classified the carotid stenosis in terms of its transversal fraction of the artery occupied by the plaque, despite of the determination is different in each study [32]. The NASCET study was used as reference for the majority of studies performed after.

2.2.1 Carotid Endarterectomy

Follow-up from medical therapy or conventional therapy groups from randomized trials of carotid endarterectomy allows some understanding of the relation between carotid artery stenosis and subsequent stroke [22]. Carotid Endarterectomy (CEA) is the surgical procedure that consists in the removal of atherosclerotic plaque from the carotid artery to restore greater blood flow to the brain [17], like is shown in Figure 2.4. As already referred, the atherosclerotic plaque formation is responsible for the appearance of neurologic symptoms due to embolization of plaque components or blood flux reduction. Several studies refer the morphology of the plaque to be a characteristic positively related to symptoms, as well as the patient's clinical history and his degree of stenosis.

CEA is one of the most common types of vascular surgery performed in the United States with over 117000 cases done annually [38]. The expected benefits of CEA to reduce the risk of stroke depend on the presence of neurologic symptoms and the degree of carotid artery stenosis [39]. Nevertheless, it is an intervention only justifiable if neurological morbidity, cardiac morbidity and mortality associated to the procedure are significantly lower then the outcome expected from the medical treatment alone [25]. The procedure intends to prevent long term complications, but is indeed responsible for the risk of stroke in a percentage of patients, being only 3% though. It consists, in its conventional approach, of exposing and mobilizing the carotid bifurcation, place clamps in the common carotid artery (CCA), external carotid artery (ECA) and internal carotid artery (ICA), identified in Figure 2.4. Thereafter, it is performed a longitudinal arteriotomy in the internal carotid, with the removal of all the stenotic lesion, connection of the $intima$ connection margins and arteriotomy closure [32].

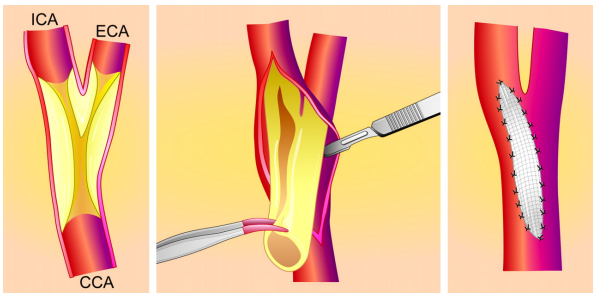


Figure 2.4: Technique of carotid endarterectomy. An atherosclerotic lesion involving the common carotid artery (CCA), internal carotid artery (ICA), and external carotid artery (ECA) is demonstrated on the left panel. The middle panel demonstrates plaque removal following a longitudinal incision of the vessel. The right panel shows the arteriotomy repair with the use of a patch [40].

For all the above reasons, and on the basis of the results of numerous published randomized trials, CEA has been established as the "gold standard" in the treatment of stenotic lesions of the extracranial carotid arteries [41].

This procedure is indicated by the Asymptomatic Carotid Surgery Trial (ACST) for patients which are younger than 75 years old and have a degree of stenosis superior than 70%, reducing the net 5-year stroke risk from about 12% to about 6% (including the 3% perioperative hazard) [42]. Possible reasons that justify the heterogeneity of opinions in clinical practice include the lack of acuity to detect asymptomatic patients with high risk of neurologic complications, continuous development in medical treatment which is believed to be much more efficient nowadays, or even financial motivations [25].

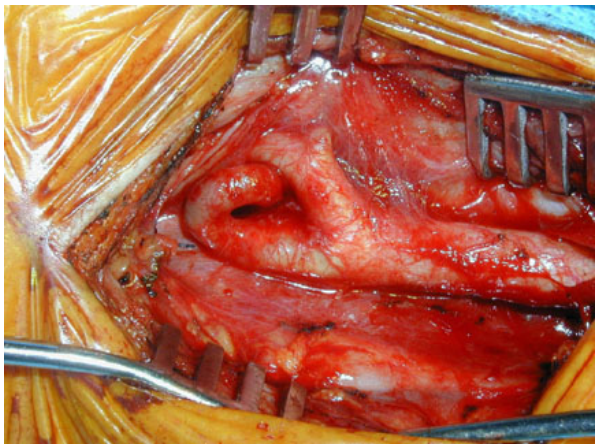


Figure 2.5: Carotid artery exposed prior to carotid endarterectomy (coil present in the internal carotid artery) [43].

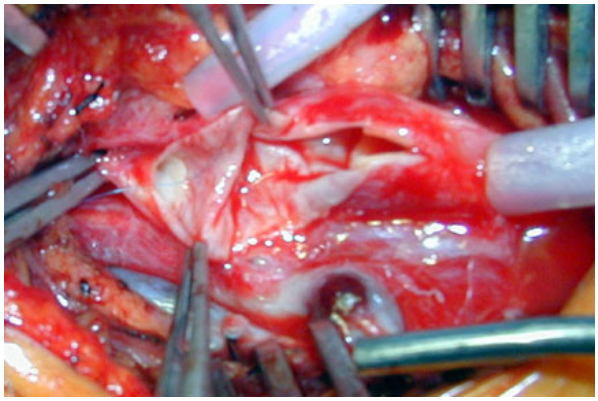


Figure 2.6: Carotid artery following endarterectomy and prior to closure (tapered endpoint and smooth appearance of the lumen) [43].

Benefit from endarterectomy depends not only on the degree of carotid stenosis, but also on several other clinical characteristics such as delay to surgery after the presenting event. Ideally, the procedure should be done within 2 weeks of the patient's last symptoms [31]. It is not a surgery absent of risk, being associated with cardiovascular and technique associated risks, having also the possibility of restenosis after a well succeeded surgery [32].

2.2.2 Carotid Endarterectomy vs. Carotid Artery Stenting

Beside carotid endarterectomy, Carotid Artery Stenting (CAS) is becoming more widely performed for the treatment of severe carotid obstructive disease, and is now accepted as a less invasive tech-

nique that may provide an alternative for selected patients, particularly those with significant comorbidities [44]. It is an endovascular, catheter-based procedure which unblocks narrowing of the carotid artery lumen to prevent a stroke, representing nowadays a valid alternative to endarterectomy.

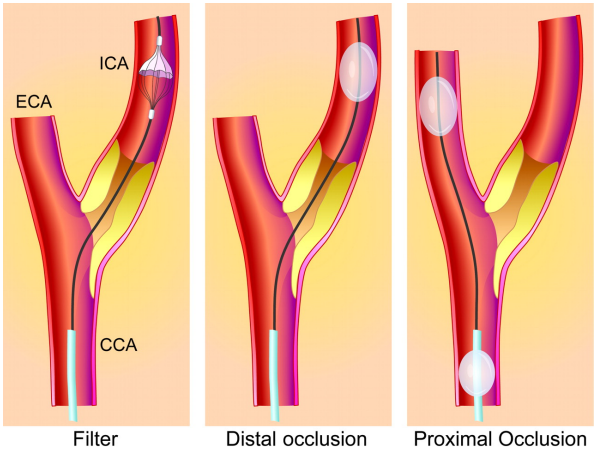


Figure 2.7: Strategies for emboli protection devices in carotid artery stenting. On the left panel, a filter device is demonstrated; in the middle, a distal balloon occlusive device; and in the right panel, a proximal occlusive device. CCA, common carotid artery; ICA, internal carotid artery; ECA, external carotid artery [40].

New endovascular procedures for treating internal carotid artery stenosis with angioplasty and stenting techniques are growing in popularity and have generated much controversy. Although the results of Randomized Control Trials (RCT)s comparing stenting with carotid surgery are mixed, and the appropriate role for stenting is uncertain, stenting is promoted as an option for patients who are deemed "high risk", "too old" or "too sick" to safely undergo CEA [38]. Nevertheless, the SAPPHIRE Worldwide registry evaluated 30-day outcomes after CAS with physicians performing the procedure after a training programme. This was the aspect that provided the procedural outcomes to become less satisfactory. They concluded that patients with indication for carotid intervention and who are anatomically high risk for endarterectomy should be offered the option of carotid stenting with cerebral protection [45]. It is once more proved by SPACE study that there are no significant differences with regard to clinical endpoints for up to 2 years after either procedure [46].

2.3 Plaque classification scores

The atherosclerotic disease and associated plaque identification and classification has been developed for several years. In 1986, a study of human atherosclerotic plaques has shown that different cell types are important for the progression of the disease [47]. In 1991, North American Symptomatic Carotid Endarterectomy Trial (NASCET) verified the utility of carotid endarterectomy in severe stenosis to surgical treatment [30]. It was then assumed, in 1993, a standard indication for carotid endarterectomy measuring [48]. It was already assumed in 1996 that degree of stenosis was not statistically related with two major determinants of plaque vulnerability, core size and cap thickness [49]. As the degree of stenosis is still, nowadays, one of the major aspects taken into account for the selection of patients for endarterectomy, it will next be explained, together with more recent scores for plaque

classification.

2.3.1 Degree of Stenosis

Carotid artery atherosclerosis is one of the main causes of stroke. It is of major importance that correct diagnosis of patients is performed, as most situations that reveal complications arise from asymptomatic plaques, more than symptomatic ones. Though degree of stenosis is a proven marker of plaque vulnerability, it is widely recognized that better risk markers for cerebrovascular events are needed [50]. It is, none the less, referred in many studies to be a good indicator of the risk of stroke [29]. The scheme already presented 2.2 addresses the groups related to the degree of stenosis diagnosed in patients by the NASCET.

2.3.2 Activity Index

Activity Index (AI) is an objective parameter of plaque echostructure that positively correlates with symptoms. AI may contribute to better selection for treatment of patients with carotid artery disease [51]. A previous study showed that a set of ultrasonographic parameters associated with degree of stenosis, were important determinants of a profile of unstable carotid plaques associated with neurological symptoms [52]. It was then given a different weight to each parameter, being AI an objective parameter that correlates with plaque instability and clinical activity [51]. It brought objectivity in the assessment of carotid plaque structure using high definition ultrasonography.

2.3.3 Enhanced Activity Index

There was, even though, the need to classify and identify a subset of plaques, considered "dangerous" for its associated high risk, as they are relevant for the indication for endarterectomy. EAI is a quantitative diagnostic measure that was developed as a score to classify asymptomatic plaques [53], being a diagnostic tool that allows to predict neurologic complications. As a consequence, the identification of a set of active plaques, that have a high neurological risk associated, helps in the indication for treatment. It results from a study [53] that enabled to identify several characteristics of a plaque, considering it as "active" by taking into account a set of parameters that are statistically relevant for separating symptomatic and asymptomatic lesions. The score is interpreted as inconclusive when EAI $= 1$, prone to produce symptoms when EAI > 1 and when there is a score of EAI < 1, the plaque will stay harmless with a significant probability, that are higher as EAI scores decrease.

EAI is then a diagnostic method that enables a decision for treatment with consequences, not only clinical, but also economical, for all the entities involved in the process.

2.4 Receiver Operating Characteristic Plots

ROC curve analysis became of great use in radar detection and experimental psychology [54]. They were suggested to be used in medical decision making, in 1967, and were used in studies of medical imaging devices, back in 1969 [55]. The selection of the optimal *cut-off* when binary

decisions are involved and one of two classes should be selected, is another aspect of its use. In Computer Aided Diagnosis (CAD) systems this tool is extensively used in the performance evaluation of the involved classifiers. ROC plots in medical decision making are commonly used as a tool which provides a direct visual comparison between tests on a common scale, does not require selection of a particular decision threshold because the whole spectrum of possible decision thresholds is included [55]. It is a useful technique for organizing classifiers and visualizing their performance [56], as well as a statistical tool to support medical decisions based on Sensitivity and Specificity analysis.

2.4.1 Accuracy as a result of Diagnostic Sensitivity and Specificity

ROC curve analysis enables the possibility of comparing diagnostic tools and determining its discriminative strength. ROC plots are a fundamental evaluation tool in clinical medicine, allowing the ability to distinguish and classify if a diagnostic method is accurate. It is important to refer that accuracy is a term used to classify weather a diagnostic tool correctly classifies subjects into clinically relevant subgroups [55], for example, health and disease, or even, operable and inoperable. To become quantifiable, the accuracy of a test can be measured for its Sensitivity and Specificity. The sensitivity of a diagnostic test is the proportion of patients for whom the outcome is positive that are correctly identified by the test. The specificity is the proportion of patients for whom the outcome is negative that are correctly identified by the test [57].

2.4.2 Evaluation of Receiver Operating Characteristic Plots

It is important to understand that when representing the results of a diagnostic test, most often, the populations overlap, as the discrimination between them is not perfect, like the representation in Fig. 2.8.

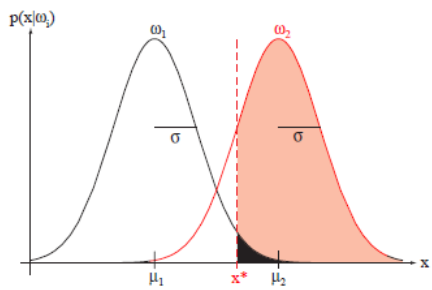
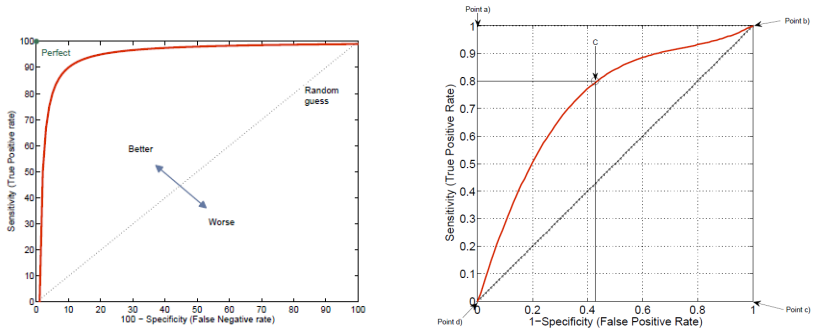


Figure 2.8: Population overlap after diagnostic test classification.

We have two populations representing, for example, the group of the population with a disease, and the other, without the disease. For every possible *cut-off* that one selects, four outcomes are possible: To correctly classify an individual as healthy (True Negative (TN)); to correctly classify an individual as unhealthy (True Positive (TP)); to classify an individual as healthy when, in fact, he is unhealthy (False Negative (FN)); finally, to classify an individual as unhealthy when, in fact, he is healthy (False Positive (FP)). Hence, one easily associates Sensitivity to the TP fraction and the Specificity to the TN fraction. ROC curves can be defined as a parametric curve, being the $Sensitivity$ a function of

$1 - Specificity$ as shown in Fig. 2.9. For every possible cut-off, a different point represents a pair with singular sensitivity/specificity. Only the entire spectrum of this points provides a complete analysis of test accuracy [55].

To better understand the dynamic of ROC plots, Figure 2.9 (b) presents four points of analysis. Together, these points represent extreme situations of ROC analysis, gathering also the best and worst case scenarios. Point a) is the best possible result. It represents a test with perfect discrimination with a ROC curve that passes trough the upper left corner (Sensitivity=1 and Specificity=1). A curve that passes through point c) misses all classifications (Sensitivity=0 and Specificity=0). It represents a classifier that indicates a healthy patient as diseased, and a diseased patient as healthy. Point b) represents a classification of all individuals as symptomatic, regardless of score (Sensitivity=1 and Specificity=0). Finally, point d) represents a classification of all patients as asymptomatic, regardless of score (Sensitivity=0 and Specificity=1). Therefore, the closer the ROC curve is to the upper left corner, the higher is the overall accuracy of the test [55]. The problem under analysis is about Sensitivity/Specificity values between 0 and 1, that results in the representation of a curve which demands further evaluation *criteria* for the selection of the appropriate cut-off value.



(a) Receiver Operating Curve example.

(b) Exemplificative ROC curve with reference points.

Figure 2.9: Receiver Operating Characteristic curves.

The procedure, and underlying criterion, to select an optimal *cut-off* is crucial for the final performance of the classifier [3]. Therefore, a test where two populations do not overlap, meaning that there is perfect discrimination, would result in a curve balanced completely to the upper left corner, where there is a maximum in sensitivity and specificity (100%). Knowing that a criterion should reflect the statistics associated with each group, it also should depend on other objective and subjective factors relevant in the whole process. The optimal *cut-off* primarily depends on the true distributions of both populations but also on the consequences associated with the decision making procedure; failing an *endarterectomy* on a patient from the *symptomatic* group is probably, from a a clinical and medical point of view, severer than making a surgical intervention on a subject from the *asymptomatic* group.

Different cut-off criteria exist in the literature. Youden's Index and ROC Area Under the Curve (AUC), considered the most commonly used global index of diagnostic accuracy [58], are two examples. These are machine learning methods that allow better operating point selection (Youden's

index) and model comparison (AUC). In the next chapter, a literature review is made to completely understand how one can make the most of ROC curve analysis, in order to properly assist medical decision making for endarterectomy.

Next section introduces the economic evaluation theme, to understand the fundamentals of economic evaluations. This will allow to explain concepts like QALY and ICER, used further in this thesis.

2.5 Economic Analysis

Evaluation of surgical procedures for carotid atheroscleroses treatment are possible in an economics perspective. It would be interesting to support the decision making process for endarterectomy in a wider perspective, complementing the medical aspects with economic and other related information.

The decision to commit resources to one use instead of another is always difficult. Scarcity of people, time, facilities, equipment and knowledge demand a sustained answer to the allocation of resources for at least three reasons [59]:

- Without systematic analysis it is difficult to identify clearly the relevant alternatives;
- The viewpoint assumed in an analysis is important;
- Without some attempt at measurement, the uncertainty surrounding orders of magnitude can be critical.

Hence, any consideration made about value for money based on economic evaluation minimizes the chances of an important alternative being excluded from consideration, or a new programme being compared to an inefficient baseline, offering the possibility of comparing between programme costs and resulting benefits. The extent to which they may contribute is based on the viewpoints considered for the analysis.
There are some limitations in economic evaluations due to the importance of the distribution of costs and consequences among different patient or population groups. This aspect is not usually incorporated into the analysis. Also, the different forms of analysis available have different approaches and different criteria, resulting in different discussions and conclusions.

2.5.1 Types of economic analysis and the concept of costs

Economic evaluations may be divided in Cost-effectiveness Analysis (CE Analysis), Cost-utility Analysis (CUA) and Cost-benefit Analysis (CBA). It is of most importance that when performing an economic study, the author identifies explicitly the perspective of the study, whether it is to assess the incremental cost-effectiveness ratio or the quantification of benefits in a monetary scale, for example. For all the possible types of analyses the concept of costs is always present, which implies the need for its correct definition. Costs (or benefits) can be assessed by the perspective of the payer, patient, provider and society. The societal perspective is the most general, but it also is the most difficult and may not provide the best answers to specific questions [60]. The cost to society is the net cost of all the

different components of society, including the patient's lost productivity and the expenses involved in giving and receiving medical care [60]. Determining the costs that should be counted is relevant and, for that matter, four types of cost can be considered: direct medical costs, direct nonmedical costs, indirect costs and intangible costs. The first ones are associated with medications and procedures, for example. Direct nonmedical costs refer to transportation, clothing and family care, for example. On the other hand, indirect costs can be linked to loss of life quality and work absenteeism. Intangible costs are difficult to quantify as they indicate the cost of pain, suffering and health gain, for example. Some of this terms have been discussed over time as inadequate. Nowadays, intangible costs, for example, are addressed through utility and willingness to pay [59].

Moreover, the type of evaluation is crucial to define the analysis parameters. A clear justification should be given for the form of evaluation chosen in relation to the question being addressed [61]. We will present the main purposes for cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis.

2.5.2 Cost-effectiveness analysis

CE Analysis measures the consequences of programmes in the most appropriate natural effects or physical units, such as *years of life gained* or *cases correctly diagnosed*, when a single effect of common interest, common to both alternatives, but achieved to different degrees is in question [59]. It is used when benefits are measured but not converted to monetary units [60] or, in other words, when two alternative treatments are being compared, assessing the costs and outcomes for each treatment and evaluating their ratio (dollars for life years gained, for example). It applies to situations where a decision maker, operating with a given budget, is considering a limited range of options, within a given field [59].

2.5.3 Cost-utility Analysis

CUA differ from the cost-effectiveness analysis by accepting multiple effects of consequences, not necessarily common to the two alternatives in question [59]. The most common measure of consequences in CUA is the QALY. It represents not only a single measure of years gained by the treatment in analysis, but also the states of health relatively valued, as shown in Figure 2.10. This means that one can assess the number of years gained when accepting the treatment and the health condition expected for those years, measured in a scale of 1 (perfect health) to 0 (equivalent to death). Numeric weights are assigned to this scale and the duration of time in each health state is multiplied by its weight. Then, the sum of weight times the duration equals QALYs [60]. The results in CUA are commonly represented by the investment required (monetary costs, for example) per QALY, allowing comparison for each method considered.

2.5.3.A Quality-adjust Life Years for Endarterectomy

The concept of QALY has the advantage of measuring health outcome, simultaneously capture gains from reduced morbidity (quality gains) and reduced mortality (quantity gains), and combining

these into a single measure [59]. It can be understood as the relative desirability of each treatment alternative, by the meaning of the life years gained by an intervention, comparing to the life deterioration of not performing medical treatment (or even comparing to applying another strategy of treatment).

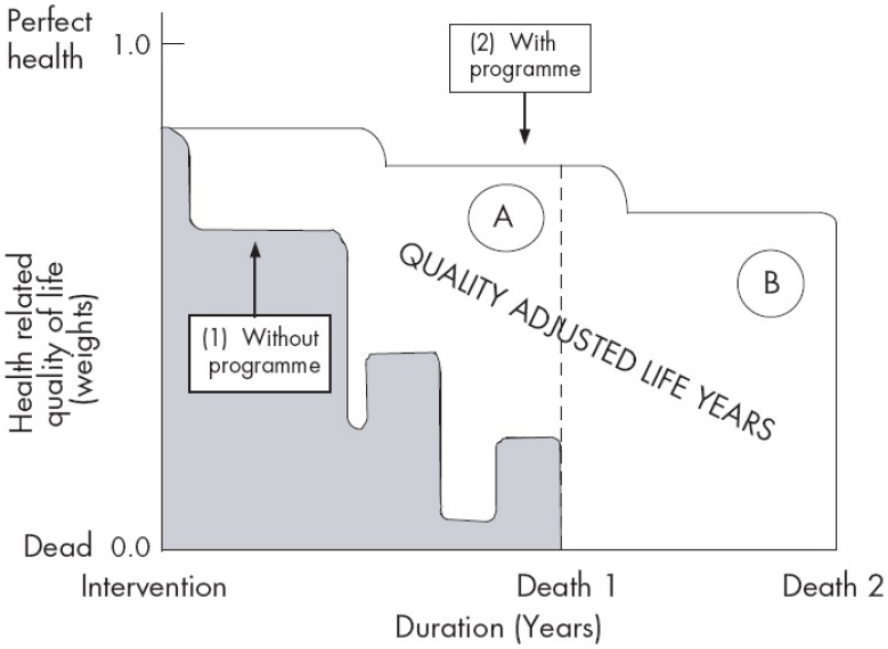


Figure 2.10: Example of Quality-adjusted life-years gained from an intervention [59].

To ensure the correct QALY concept, the quality weights must be based on preferences, with a correct scale implementation where the ends are fixed by death (with a value of 0) and perfect health (with a value of 1). The calculation of the QALYs for an intervention is made by the quality weight attributed to a health state, multiplied by the time (usually in years) that the patient stays in that state.

The appropriate comparison between two health care programmes or interventions is in terms of ICER [59]. This is the most popular method of presenting the results of cost-effectiveness and cost-utility analysis. By definition, ICER represents the cost needed to produce an additional QALY and is presented as the ratio between additional costs per QALY gains.

2.5.4 Cost-benefit Analysis

CBA is characterized by the presentation of consequences of health care programmes in monetary units. Contrarily of CUA where the benefits have their own scale, in CBA the results can be presented in dollars, for example, enabling the analyst to make a direct comparison of the programme's incremental cost with its incremental consequences [59]. Associated to this analysis is always the possible conclusions of how much it is worth to pay, for the incremental positive result obtained. Most of the time is associated to the "willingness-to-pay" in order to achieve or avoid a given outcome [59]. It allows a broader utilization than CE Analysis and CUA, as it is not restricted to comparing programmes within health care. Despite the apparent advantages of CBA, they have the practical problem of valuing benefits, such as the saving of life or relief of pain, in money units [61].

2.5.5 Final considerations

The presented information is important when one pursues an informed decision making process. We can include economical information about carotid endarterectomy to the decision process of a patient with carotid atherosclerosis. When not only aspects of the patients diagnosis and state of health are considered, but also, the effects and costs of an intervention, it is understandable that either the patient and the health care provider will benefit. We presented here the different alternatives of economic analysis in order to, further in this thesis, understand the bibliography existent about carotid endarterectomy economic analysis and to make the best use of it. Next chapter will present a literature review about ROC curve analysis and also, economic studies for endarterectomy.

3

Literature Review

Contents

In this chapter is presented a literature review about ROC curve analysis, in order to understand its usage in the process of decision making for health care programmes. The information collected from the literature is summarized, enhancing the strong points and weaknesses of some ROC evaluation methods. Economic evaluations on endarterectomy are also addressed in this chapter. Its inclusion in this thesis comprises the understanding of the economic analysis types usually used, the type of costs considered and the effects in which the analysis are grounded.

3.1 Introduction

It is consensual that the correct diagnosis of the atherosclerotic plaque is of most importance to perform a sustainable decision for endarterectomy. Nevertheless, the correct classification of an individual as symptomatic or asymptomatic associating medical diagnosis, hospital characteristics at the time of decision, economic aspects and other logistic variables, may result in an improvement for endarterectomy decision making supported with economic analysis and ROC analysis.

The bibliographic review for this chapter was mainly based on the literature available in online databases, such as NCBI, PubMed and Stroke, from the American Stroke Association. These databases were searched using queries such as “Carotid endarterectomy”, “ROC curves”, “ROC cut-off”, “ROC evaluation” in the context of ROC curve analysis and “CEA economic evaluation”, “Carotid endarterectomy costs and benefits” and “QALY for endarterectomy” in the context of economic analysis of endarterectomy. It was possible to expand the scope of the research from the references and citations tools found in the referred databases.

3.2 ROC Evaluation Methods

As already referred, ROC plots are a useful tool for assessing the performance of diagnostic tests. These tests are evaluated through their ability to diagnose the outcome correctly, which in our case, means classifying an individual as symptomatic or asymptomatic correctly.

3.2.1 Youden’s Index

The Youden Index (J) is a method to investigate cut-off values from a range of different decision thresholds, in order to decide which value should be used to discriminate between patients according to outcome [57]. It is a much appreciated method by physicians in terms of simplicity and clarity [62]. Nevertheless, as shown in table 3.1, most of the times, its usage is made considering equal importance to sensitivity and specificity. This downside misses the fact that missing a positive diagnosis, resulting in a false negative outcome, may be greater than missing a negative diagnosis, resulting in a false positive outcome. This type of error must be weighed from aspects like the population’s predisposition for a certain disease, minimizing the global error of the classifier, resulting in a larger number of correctly classified individuals. Weighing is needed to optimize the index J [63].
The simplicity of this method results from its capacity of determining the overall diagnostic effectiveness with the simple usage of sensitivity and specificity, like the criteria represented in Table 3.2

Table 3.1: ROC evaluation methods for classifier performance and best operative point selection.

Study	First Author	Method	Analyzed Criteria	Final considerations
Statistics Review: Receiver Operation Characteristic Curves [57]	Bewick, V.	Youden's Index	J=Sens + Spec - 1	Sensitivity and specificity may depend on characteristics of the population (age, severity of the disease).
		ROC AUC	Sum of the areas of trapeziums Difference between x-values multiplied by half the sum of the y-values.	Trade-off between sensitivity and specificity is not objective.
Ultrasound plaque EAI for predicting neurological symptoms [53]	Seabra, J.	ROC AUC	Area between ROC curve and the no-discrimination line Higher score given to positive example, rather than negative example, when randomly picked.	Relative importance of TPR and TNR should change accordingly to each scenario.
		DDIC	TPR=1-FPR (=) Sens(c)=Spec(c) Intersection of ROC curve with the line at 90 degrees to the no-discrimination line.	Cut-off should be chosen accordingly to a justifiable criterion.
ROC graphs: Notes and practical considerations for researchers [56]	Fawcet, T.	ROC AUC	Equivalent to the probability that the classifier will rank a randomly chosen negative instance.	Reduces ROC performance to a single scalar value representing expected performance. Used when general measure of predictiveness is desired.
Revisiting Youden's index as a useful measure of the misclassification error in meta-analysis of diagnostic studies [62]	Böhning, D.	Youden's Index	Maximize sum of sensitivity and specificity (Sens+Spec=1+J)	Characterized for its simplicity and clarity.
			One of the points of intersection between the two normal distribution curves describing diseased and healthy population.	Provides maximal proportional reduction of expected regret.
Optimal cut-point and its Youden's index [63]	Schisterman, E.	Youden's Index	J=maxsens+spec-1 Maximum vertical distance of difference between the ROC curve and the diagonal or chance line.	Weighting is needed to optimize J. The loss from missing a case may be greater than from evaluating control.

suggest. On the other hand, a visual perspective is possible using ROC plots. Also, the maximization of sensitivity and specificity, using the assumption that they have equal relative importance, can be calculated graphically [63]. It represents the maximum vertical distance of the difference between the ROC curve and the chance line.

3.2.2 Descending Diagonal Intersection Criterion

Descending Diagonal Intersection Criterion (DDIC) represents the intersection of the ROC curve with the line at 90 degrees to the no-discrimination line, or chance line. This is an heuristic method considered to investigate the cut-off providing the best discriminative power of a test (or predictive method) [53]. The optimal cut-off is selected in order to make *Sensitivity* (True Positive Rate (TPR)) equal to *Specificity*, $Sens(c) = Spec(c)$, where it is assumed that we want simultaneously, and with the same cost, increase the TPR parameter and decrease the False Positive Rate (FPR). From a geometrical point of view the optimal *cut-off* is the one where the ROC curve intersects the descending diagonal. Like it is mentioned for the Youden Index, also in DDIC the relative importance of TPR and FPR should change according to different scenarios. The consequent cut-off, obtained from the interpretation of the Sensitivity and Specificity values, should be chosen under a justifiable criterion. It should not consider that the best diagnostic outcome is provided by the classifier that maximizes Sensitivity and Specificity values, giving equal importance to both, as the only discriminative parameter.

3.2.3 ROC Area Under the Curve

Observing table 3.1, one can realize that several criteria are used to calculate the area under a ROC curve. Its usage is widely spread in several areas of interest like, for example, machine learning for model comparison and medical decision making. This method enables the possibility of comparing classifiers reducing ROC performance to a single scalar value, representing ROC performance [56]. The interpretation of AUC values is straightforward as it is a portion of the area of a unit square. Its value is always between 0, as the worst possible result, and 1, which represents a perfect classifier. Random guessing produces the diagonal line between (0,0) and (1,1), which has as an area of 0.5 [56]. Hence, results under 0.5 would represent a classifier with no discriminative power. The score of a certain AUC analysis can be based on other criterion, which assigns higher score to a positive example, rather than a negative example, when randomly picked [53].
There is a simple computation process that adds successive areas of trapezoids to a variable. Those trapezoids correspond to the areas between each point in the ROC curve. The final value of that variable is then divided by the multiplication of positive examples and negative examples, in order to scale the value to the unit square. For the same purpose, it can be understood as the difference between x-values multiplied by half the sum of the y-values [57]. Though useful for diagnostic tool comparison and evaluation, this measure does not inherently lead to benchmark optimal cut-points for clinicians and other health care professional to differentiate between diseased and non-diseased individuals [64].

Table 3.2: Various methods for decision making support based on ROC analysis

Method	Criterion	Purpose	Advantages	Disadvantages
Accuracy	$\frac{TPR+p\times(1-FPR)}{1+p}$	Probability of a correct test result, measure of ability to discriminate between two subclasses of subjects	Weighed average of sensitivity and Specificity, with weighs equal to prevalence (and prevalence (p) complement).	Equally undesirable False Positive and Negative outcomes. Index for a single threshold
Efficiency	$Eff(c) = [p \times Sens(c) + (1-\lambda)Spec(c)] \times 100\% or Eff = \frac{TP+TN}{TP+TN+FP+FN}$	Number of correctly classified individuals	Simple computation and easy to understand	Index for a defined threshold and prevalence
Precision	$\frac{TPR}{TPR+p\times FPR}$	Reproducibility of the quantitative results	Imposes a varying effective skew-ratio	Weakly skew-sensitive
Youden's index	$J = max(Sens + (Spec - 1))$	Operating characteristic furthest from random classification, reflects the intention to maximize the correct classification rate	Widely used in medical decision making, easy to implement	Prevalence independent, FP and FN equally undesirable
Sensitivity at fixed FPR	—	Cut-off is selected accordingly to specific clinical setting	Enables decision making based in specified objectives, focus on particular portion of ROC with clinical relevance at that stage	Cut-off selection is fixed and only related to Specificity, FPR should be chosen before
Area Under the Curve (AUC)	—	Measure of overall performance	Relevant for classifier comparison and to assess classifier discrimination capacity	Prevalence independent, no cut-off selection
Partial AUC	—	Application of ROC AUC in a particular portion of the curve, compromise between AUC and Sensitivity at fixed FPR	Allows to focus on the portion of the curve relevant to a particular clinical application	Selection of partial area of analysis, no cut-off selection
Likelihood ratio	$LR(+) = \frac{Sens}{1-Spec}$ or $LR(-) = \frac{1-Sens}{Spec}$, Slope of the ROC curve	Expression of probability of test results, given the presence and absence of disease	Can be calculated for a single test value, for results in a defined interval or for results on one side of a particular threshold. Minimal information needed to revise prior disease probability	Does not locate the operating point on the curve
Positive Predictive Value	$PPV = \frac{TP\times p}{(TP\times p)+FP(1-p)}$	Post-test probabilities	Function of both intrinsic accuracy and prevalence of the condition	Do not select operating characteristic point
Negative Predictive Value	$NPV = \frac{(TN)\times p}{(1-p)FN+p\times TN}$	Post-test probabilities	Function of both intrinsic accuracy and prevalence of the condition	Do not select operating characteristic point

3.2.4 Other ROC evaluation criteria

Table 3.1 refers to other criteria and rates like accuracy, efficiency, precision, Likelihood Ratio, Positive and Negative Predictive Values. These allow a better understanding of ROC interpretation. Accuracy measures the ability of a test to discriminate between two subclasses of subjects. Efficiency is the number of correctly classified individuals, with the possibility of being presented as a percentage value. Precision indicates the reproducibility of the quantitative results of a classifier. Likelihood ratio is the expression of whether a test result usefully changes the probability that a condition (such as a disease state) exists. Positive and Negative predictive values are the post-test probabilities, which combines intrinsic accuracy and the prevalence (p) of the disease. The prevalence of the disease for the Portuguese reality was studied in 1991 by José Fernandes e Fernandes, Luis Mendes Pedro et al. [65]. The study showed a global prevalence for the referred disease of 31.8%, from a population of 1143 patients of the Vascular Laboratory. This prevalence is representative of a population of patients sent to Instituto Cardiovascular de Lisboa (ICVL) by other health services like Neurology or Cardiology. Further in this thesis, we will try to understand how these rates can be used to better justify the decision process for endarterectomy.

3.2.5 Final Considerations

The presented methods to select optimal cut-off values do not consider aspects like population predisposition for the disease, population age and procedure costs for example. The cut-off value should be chosen accordingly to a justifiable criteria, where aspects like hospital resources, human resources, financial motivations and year seasoning. Also, should one be worried about sparing as many patients as we can from surgery? Is it more important to identify and treat all subjects that will develop a neurological complication, even though a large number of patients must be operated? Or, should one decide upon combining low false positive rates and false negative rates? All these aspects reveal that the trade-off between sensitivity and specificity of a diagnostic tool is far from objective.

3.3 Economic Analysis of Carotid Atherosclerosis Treatments

This section of the thesis aims at understanding which type of economic analysis is more common and what are the costs considered, for endarterectomy purposes. The QALYs used in the literature are presented, in order to understand the utility values considered for endarterectomy and associated states of health. For carotid atherosclerosis there are medical therapy and surgery as treatment possibilities. Many studies present comparisons between CEA and CAS. Economic evaluations are commonly used to assess the characteristics of these two procedures, most of the times, trying to realize which one is more efficient than the other, cost-effective or simply compare costs and benefits. Table 3.3 summarizes the studies gathered in the context of economic analysis for endarterectomy. It was enhanced the type of costs considered in each study and how they were collected, the methodology used and the main conclusions of the authors.

As shown in Table 3.3, several methodologies were adopted and most of the studies presented

Table 3.3: Review of Economic studies for Carotid Endarterectomy

Study	Author	Year	Surgical intervention	Objectives	Methodology	Costs Considered	Principal conclusions
Dollars and Sense: The economics and outcomes of patients undergoing CEA [66]	Hodby, D.	2002	CEA	Examine the costs and outcomes of patients undergoing CEA who returned directly to the vascular unit, rather than ICU/HDU. Determine possible cost reductions	Tracking patients clinical pathway from admission to discharge. Data used from case audits, informal interviews of patients. Costing data from diagnosis-related groups (DRGs) Comparison between costs in ICU and ward.	Direct staff Cost per patient considered: drugs, nursing, medical, others.	Development of guidelines and protocols allows to allocate patients to the ward, rather than the ICU/HDU, after surgery. Mainstains consistent standard of care at the least cost and eith the best outcomes. Decreased length of stay.
Hospital resource use following CEA in 2006: Analysis of the nation wide patient sample [67]	Young, K.	2010	CEA	Explore relationships among patient age and LOS for CEA Analyze hospital costs regarding CEA Discharge disposition following CEA	Primary outcome was LOS from procedure to discharge. Secondary analyses studies total LOS, hospital costs and discharge disposition.	Used cost-to-charge ratios to compensate charged costs. Total costs associated with CEA per discharge record.	Hospital LOS and costs following CEA increased with increasing patient age.
Costs and Benefits of carotid endarterectomy and Associated Perioperative Arterial Imaging [68]	Benade, M.	2002	CEA	Critically appraise the studies addressing the economic complication of CEA and and Associated Perioperative Arterial Imaging	Identify health economics research articles on the evolution of the costs and benefits of CEA.	Cost per life-year gained, cost per QALY, incremental cost effectiveness ratios, cost per CEA and cost per imaging investigation	The cost effectiveness of CEA and perioperative investigation remains unclear for several reasons. Cost estimates from different studies were not consistent. Comparison between studies is difficult because of terminology out of context.
Is carotid angioplasty and stenting more cost-effective than carotid endarterectomy? [41]	Kilaru, S.	2003	CEA vs. CAS	Precise comparative analysis of the immediate and long-term costs associated with CAS and CEA	A Markov analysis model was created to evaluate the relative cost effectiveness of CEA and CAS.	Procedural costs, Cost of morbidity, Quality adjusted life expectancy, QALY (costs were evaluated, rather than charges	CEA is cost saving compared with CAS It is recognized that morbidity, mortality and costs will vary between surgeons and institutions. Results associated with CAS may improve over time.
Economic evaluation of CAS vs. CEA for treatment of carotid artery stenosis [69]	Pawaskar, M.	2007	CEA vs. CAS	Compare hospital costs and reimbursement for CAS and CEA	The Richard M Ross Heart Hospital clinical and financial databases were used to obtain patient specific info and procedural charges. Cost data were generated by applying the hospitals' ratio of cost to charges for all DRG charges.	Procedural, Nonprocedural	Total cost of CAS is twice the cost of CEA. Mean nonprocedural costs of CAS are lower. Savings per patient from reimbursement are greater for CEA than CAS.
Cost and cost effectiveness of CAS vs CEA for patients at increased surgical risk [1]	Mahoney, E.	2011	CEA vs. CAS	Evaluate the cost-effectiveness of carotid stenting vs. CEA using data from the SAPPHIRE Trial among patients at high surgical risk	Patients with na accepted indicator for CEA but at high risk of complications were randomized to underwent CAS or CEA. Clinical outcomes, costs, resource use and quality of life were assessed prospectively for 1-year period. Life expectancy, quality adjusted life expectancy and health care costs were estimated.	Costs were calculated as the product of resource use and unit cost for each component. Acquisition costs for each item were estimated. Hospitalization costs were registered based on billing data. Outpatient procedures costs. Nursing costs. Rehabilitation costs.	Carotid stenting with embolic protection is more costly than CEA. Stenting is na economically attractive alternative to endarterectomy for patients at high surgical risk.
A cost-effectiveness analysis of carotid artery stenting compared to endarterectomy [34]	Young, K.	2010	CEA vs. CAS	Determine cost-effectiveness of carotid artery stenting compared to CEA in symptomatic subjects who are suitable for either intervention	Markov analysis of the two surgical procedures using Medicare costs Analyze characteristics of a symptomatic 70-year-old cohort over a lifetime.	Direct medical costs Direct Medicare Costs ($2007)	CEA remains the optimal intervention CEA has lower direct costs
Cost-effectiveness of endarterectomy in patients with asymptomatic carotid artery stenosis [27]	M. Henriksson	2008	CEA vs. Best Medical Treatment	Assess if endarterectomy in addition to best medical management is recommended to patients with asymptomatic carotid artery stenosis.	Decision-analytical modelling for expected costs and health outcomes based on ACST.	Costs were based on 2006 prices and were adjusted by means of consumer price index.	Carotid endarterectomy in addition to best medical management can be considered cost-effective in men aged 73 years or less.

are CE Analysis. We shall highlight the type of costs considered, the effects in terms of QALY and the ICER, when presented.

Firstly, the type of costs considered differ, as some studies collected costs from discharge records and others used direct reference costs, as Young et al. [34] based on direct Medicare costs. It is common to divide the costs considered in procedural and non procedural. From the presented studies, the estimation of cost per endarterectomy varies from $6636.35 to $11500. This variation in costs is explained, apart from different considerations of direct and indirect costs like procedural costs, drugs, nursing and others, by the complexity of the treatment (resources used) and results of the surgery for each patient. Hodby et al. [66] divided their study results in three groups: carotid surgery with major complications, carotid surgery with nonmajor complications and carotid surgery with no complications. The results showed differences of cost per surgery of approximately $4000.

Secondly, being most of the studies presented CE Analysis, they also enhanced the health outcome for the patients, in terms of quality-adjusted life years (QALY). Table 3.4 summarizes this information for a more comprehensive review.

Table 3.4: Review of Economic studies for Carotid Endarterectomy in terms of their outcomes and main conclusions.

Author	Year	Type of patient	Median Age	Outcome (QALYs)	ICER (cost/QALY)
Kilaru	2003	Symptomatic	70		$4600
Young, K.	2009	Symptomatic	70	9,64	
Mahoney, E.	2011	Symptomatic (>50% Stenosis) or Asymptomatic (>79% stenosis)	72		$6555 (Stenting vs. CEA)
Henriksson, M.	2008	Asymptomatic, Men	65	8,477	34.557€(CEA vs. BMT)
		Asymptomatic, Women	65	8,378	311.133€(CEA vs. BMT)
		Asymptomatic, Men	75	5,929	58.930€(CEA vs. BMT)
		Asymptomatic, Women	75	5,97	779.776€(CEA vs. BMT)
Khan, A.	2012	Symptomatic or Asymptomatic (>69% stenosis)	60-80	0.702	$229429 (Stenting vs. CEA)

Despite the QALYs scale being from 0 to 1, QALYs values in Table 3.4 are above 1 because they were multiplied by the average life expectancy for the patients. Some studies presented are comparisons between endarterectomy and carotid stenting, but Henriksson et al. [27] presented a study that compares endarterectomy to the best medical treatment (BMT) available. Mahoney et al. (2011) [1] evaluated the cost-effectiveness of carotid stenting versus carotid endarterectomy using data from the SAPPHIRE trial. Patients were followed for a 1-year period and life expectancy, quality-adjusted life expectancy and health care costs beyond the follow-up period were estimated. The ICER for stenting compared with endarterectomy was $6,555 per QALY gained. We shall also consider the CREST trial (Carotid Revascularization Endarterectomy versus Stenting Trial) analysis made by Khan et al. [70]. They estimated the QALYs associated with each treatment modality, by adjusting for the incidence of each quality-adjusted outcome (QALY weights of ipsilateral stroke, Myocardial Infarction (MI), death, and postprocedure QALYs) and ICER was estimated for the 4-year period after the procedure. These led to 0.702 QALY for CEA (ranging from 0.0 [death] to 0.815 [no adverse events]). Kilaru et al. (2003), presented a study that compared two types of surgery: CEA and CAS. The analysis was performed for immediate and long-term costs associated, in the form of a CE Analysis. The authors determined a long term service rate in QALYs and lifetime costs for a hypothetic 70-year-old cohort undergoing CEA and CAS. However, the concept of cost-saving does not completely represents the initial purpose and the analysis of cost-effectiveness was not entirely discussed. Young et al. verified

that Length of Stay (LOS) increased with age and average cost associated with CEA was $10965 [67]. However, the study does not mention which aspects were taken into consideration. Also in 2010, Young et al. [34] presented a cost-effectiveness analysis of carotid artery stenting compared to carotid endarterectomy in symptomatic subjects who were suitable for either intervention. Direct Medicare costs were used (2007 $USD) and considered characteristics of a asymptomatic 70-year-old cohort. The results mentioned that lifetime costs were $35200 and QALYs were 9.64 for CEA. In the case of CAS lifetime costs were $52900 and the associated QALY gain was 8.97.

3.3.1 Summary

One observes from the presented articles that the costs mentioned in each study were collected differently. The costs registered were from different sources like the patient's discharge records, the cost-to-charge data and billing data. It is common to differ the actual costs from the charges imposed to the patients, for the fact that the actual value paid by the patient/insurance company is not the same as the real cost the health service provider actual pays. Also, for the acquisitions of material, [1] used an estimation. Like this, it is common that the conclusions presented in the studies do not converge. Despite most of the studies are based in a CE Analysis, the windup views from different authors led to other aspects, like the relation between patient age and LOS which is an intermediate conclusion. From the purpose of this section, we enhance that there is usable information for the present work. The studies from Henriksson [27], Mahoney [1] and Khan [70] are recent and represent the type of results needed. The division of patients by age and condition (symptomatic vs. asymptomatic), as well as, the presentation of utility values for each state of health, serve the intent of the present work.

4

Methodology

Contents

In this section will be addressed aspects about subject classification and the usage of ROC plots as a decision making support tool. The main goal is to understand how to correctly classify a subject when dividing the population in classes. Firstly, a general consideration of subject classification is made, giving the motivation for the problem in analysis. The problem formulation is presented. Secondly, we follow the theme of endarterectomy, addressing the analysis to a binary classification problem. This will be made from two perspectives: medical and engineering point of view. By the probabilistic approach we consider the mathematical aspects of each criterium. Using ROC plots we intend to have a graphical perspective common in medical usage. The attempt of creating a bridge between these two perspectives is made to allow a wider understanding on the subject. Different criteria for ROC analysis are addressed and detailed. Also, economical information for endarterectomy is presented, in order to complement the analysis.

4.1 Introduction

It is now clear, regarding the guidelines discussed in the previous chapters, that medical decision sustained by CAD tools and other support tools for the decision making process, will allow better reproducibility and objective results. Previous chapters also provided insight on the most common methods used in ROC plots evaluation. The diagnostic performance of a test, or the performance of a test to discriminate diseased cases from normal cases is evaluated using ROC curve analysis [55]. They are also used to compare the diagnostic performance of two or more classifiers. Hence, a worthwhile analysis about sensitivity and specificity (for each decision point), as well as, associated population distribution probabilities are key aspects of our methodology. In fact, considering the given data, when fixing a decision point becomes possible to determine the probability of a true positive and of a false positive. The principles of varied methodologies, that are found in the literature addressing ROC curve analysis, do evaluate a given classifier for its performance. Though, none of these methodologies provided a method answering to *a priori* knowledge of population behavior or incidence. It is also important to consider a more flexible evaluation of patients, given the physiologist experience, time line, economical and logistical aspects. A methodological framework is proposed.

4.2 Problem Formulation

Our goal is to correctly classify a patient into specific populations and consequently, choose the appropriate decision threshold value for the decision making process. This decision point will, from now on, be referred as cut-off. For every possible cut-off point or criterion value you select to discriminate between the two populations, there will be some cases with the disease correctly classified as positive (TPF = True Positive fraction), but some cases where the disease will be classified as negative (FNF = False Negative fraction). On the other hand, some cases without the disease will be correctly classified as negative (TNF = True Negative fraction), but some cases without the disease will be classified as positive (FPF = False Positive fraction) [71]. The referred classifications are usually presented in a contingency table, also called confusion matrix [72].

The Sensitivity of a diagnostic test, also called *True Positive Rate* (TPR), is defined as $TPR = \frac{TP}{TP+FN}$. It can be understood as the probability of classifying a subject as positive, when the disease is present. Specificity [53] is defined as $Specificity = 1 - FPR$ where $FPR = \frac{FP}{TN+FP}$. It is the probability that a test result will be negative when the disease is not present.

In the specific case of endarterectomy, a binary classification problem, two classes are considered: ω_S and ω_A containing the subjects that will present symptoms in the future and that will continue asymptomatic, respectively. The main goal concerning endarterectomy is to decide what class a given subject belongs to. Based on the respective *Enhanced Activity Index* (EAI) score, patients are classified as symptomatic or asymptomatic. Hence, it is expected with real data that the distributions overlap, as one rarely observes a perfect separation between the two groups.

A close analysis of cut-off $criteria$ is necessary in order to correctly decide which criterion is most appropriated for different situations. The *Descending Diagonal Interception Criterion* (DDIC) and Youden's criterion, already addressed in [3] are two examples of how one can select the most appropriate cut-off. They will now be analysed in a graphical receiver operating characteristic approach. For the present work, it is necessary to understand cut-off selection by the need of correctly classifying patients as symptomatic or asymptomatic, but also, to adjust that classification with economic aspects. We introduce a possibility that considers different weighing in Sensitivity(TPR) and Specificity (1-FPR) values, providing adjusted cut-off values.

4.2.1 Sensitivity/Specificity and associated criterion value

For the time line that exists in patient treatment, it is important to decided in each moment, which action to take. Like this, correspondent cut-off values should be used in order to classify properly a patient as symptomatic or asymptomatic. For example, when a patient first arrives in a clinic, one should strongly consider as hypothesis that the patient is symptomatic, as means to guarantee further diagnosis, leaving no doubt when classifying in the future the patient as asymptomatic. When more information is available and treatment is necessary, cut-off selection should be more demanding. This would prevent surgery as the first solution, leaving other less risky treatment possibilities as an option (higher Specificity). If further diagnosis and evaluation reveals a severe situation or any blockage that threatens muscle or skin tissue survival, then the cut-off used for patient classification should result in further interventions (higher Sensitivity). Fig. 4.1 shows the referred trade-off and expected relative value of Sensitivity and Specificity for different values of the cut-off criterion.

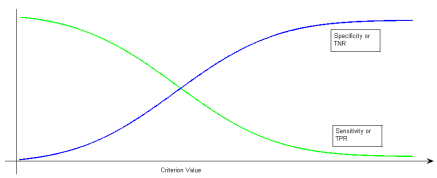


Figure 4.1: Representation of Sensitivity and Specificity behaviour for different criterion values.

These examples can be interpreted mathematically as [71]:

- When you select a higher criterion value, the false positive fraction will decrease with increased specificity but, on the other hand, the true positive fraction and sensitivity will decrease.
- When you select a lower criterion value, then the true positive fraction and sensitivity will increase. On the other hand, the false positive fraction will also increase and, therefore, the true negative fraction and specificity will decrease.

This considerations make possible the adjustment of the cut-off for patient classification. This classification can be made taking in account that the physiologist may want to analyse a specific number for the TPR as threshold, which would result in cut-off C_1. Moreover, if the risk associated to the decision is high, the physiologist might want to analyse a specific number for the FPR, which would result in cut-off C_2.

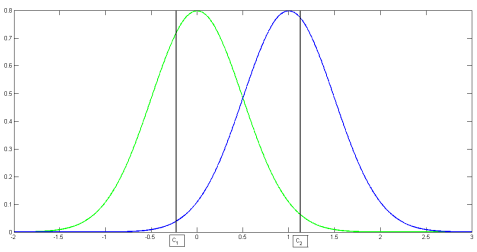


Figure 4.2: Representation of cut-off points (C_1 and C_2) considering fixed values of Sensitivity and Specificity, in the probabilistic distribution space.

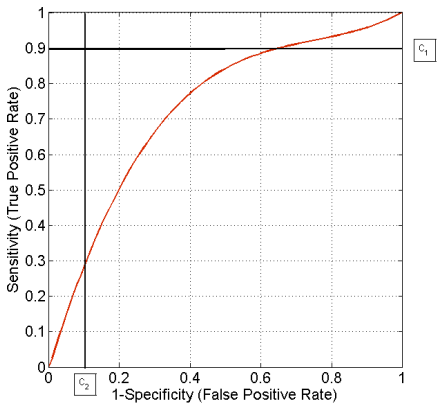


Figure 4.3: Representation of cut-off points (C_1 and C_2) considering fixed values of Sensitivity and Specificity, in ROC space.

4.3 Probabilistic Distribution Approach

Mathematically, the TPR and FPR, as well as other performance classifier measures, may be directly derived from the statistical distributions of both populations. So, let us define *True Positive Rate* (TPR), *False Positive Rate* (FPR), *True Negative Rate* (TNR) and *False Negative Rate* (FNR) as the following integrals displayed in Fig.4.4,

$$TPR = \int_{c}^{\infty} p(x|omega_S)dx \qquad FPR = \int_{c}^{\infty} p(x|omega_A)dx$$
$$TNR = \int_{-\infty}^{c} p(x|omega_A)dx \qquad FNR = \int_{-\infty}^{c} p(x|omega_S)dx. \tag{4.1}$$

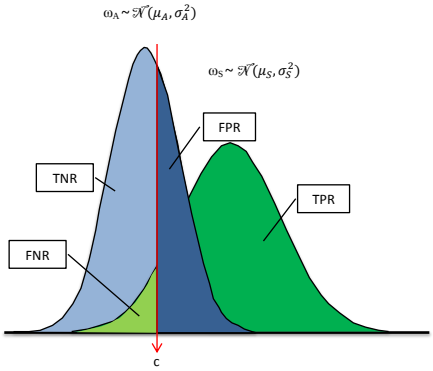


Figure 4.4: Representation of probabilistic distribution of a clinical score for symptomatic (ω_S) and asymptomatic patients (ω_A). Consideration of the possible outcomes for a given cut-off (c).

Any decision threshold c will determine the probability of a positive (the dark green area under the ω_S curve, above c) and of a false positive (the dark blue area under the ω_A curve, above c). If we have a large number of trials (and we can assume the cut-off (c) is fixed, albeit at an unknown value), we can determine probabilities of true positives and false positives experimentally, in particular the TPR and FPR.

Usually, the main goal of automatic strategies for *cut-off* selection, is to minimize the decision error rate. In the complex problem of medical decision making, in particular endarterectomy, a simple error rate minimization criterion is not appropriated. There is no gold standard for the selection of the cut-off value (c). The ROC curve analysis is an approach that enables cut-off selection accordingly to different parameters.

4.3.1 *Descending Diagonal Intersection Criterion* (DDIC)

In the first criterion considered in this paper, the optimal cut-off is selected in order to make *Sensitivity* (TPR) equal to *Specificity*, $Sens(c) = Spec(c)$, where it is assumed that we want to simultaneously, and with the same cost, increase the TPR and decrease the FPR.

This criterion may be formulated using equations 4.1 as

$$\begin{aligned} TPR = 1 - FPR \leftrightarrow \int_{c}^{\infty} p(x|\omega_S)dx &= 1 - \int_{c}^{\infty} p(x|\omega_A)dx \Leftrightarrow \\ \Leftrightarrow C_S(x) &= 1 - C_A(x) \end{aligned} \tag{4.2}$$

The optimal solution provided by this criterion, represented in Fig.4.5 corresponds, as previously shown in equation (4.2), to the intersection of the cumulative distribution associated with the symptomatic group $C_S(x)$, with $1 - C_A(x)$, where $C_A(x)$ is the cumulative distribution associated with the asymptomatic group. When $C_S(x) = 1 - C_A(x)$ we obtain the best cut-off value c^* for this criterion.

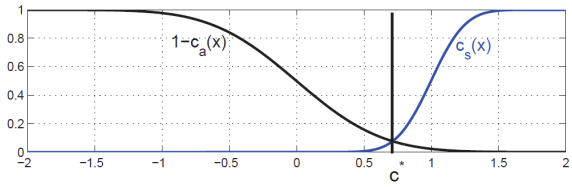


Figure 4.5: Representation of optimal cut-off point (c^*) with DDIC, in the cumulative probabilistic distribution space

The considered results have not taken into account the possibility of weighting differently the TPR and the FPR. They implie that the prevalence in the target population is 50% and that the costs associated to false positives are equal to false negatives. In general medical applications, the cost associated with TPR is different from FPR, hence weighting them differently is a useful feature. Accordingly, let us consider the cost variable λ in our criterion, and expand equation 4.2, such that:

$$\begin{aligned} \lambda \times TPR &= (1-\lambda)(1-FPR) \\ \lambda \times \int_c^{\infty} p(x|\omega_S)dx &= (1-\lambda)(1-\int_c^{\infty} p(x|\omega_A)dx) \end{aligned} \tag{4.3}$$

For easier interpretation, the presented calculations will provide a direct graphical and geometrical analysis of the interception line, which allows the selection of the cut-off. Like this, equation 4.3 can be presented as

$$C_S(x) = \frac{1-\lambda}{\lambda}(1 - C_A(x)) \tag{4.4}$$

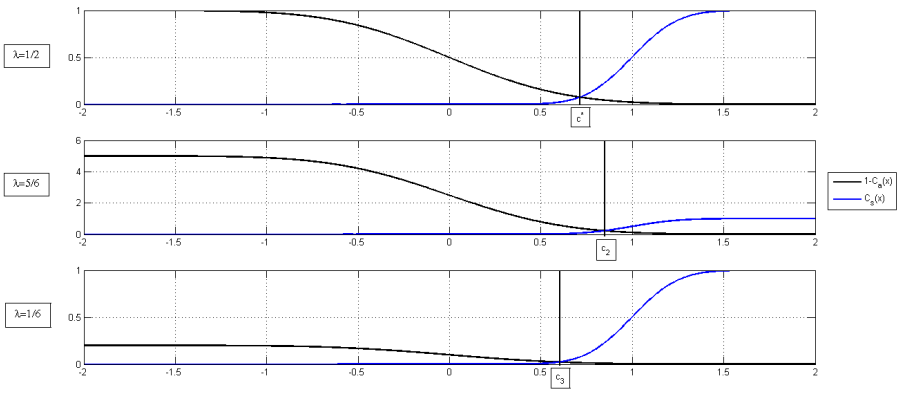


Figure 4.6: Representation of optimal cut-off points (c^*, c_2 and c_3) with DDIC, in the cumulative probabilistic distribution space for different λ weights.

4.3.2 *Youden Criterion* (YC)

Youden's index [63], depending on the *cut-off* parameter c, is defined as $J(c) = Sens(c)+Spec(c)-1$ or $J(c) = TPR(c) - FPR(c)$. The optimal *cut-off* under the Youden criterion is the maximizer of the Youden index according to

$$c^* = \arg\max_c J(c) \tag{4.5}$$

Considering the distributions of both populations and the integrals represented in Fig.4.4 this criterion is formulated as follows

$$\begin{aligned} J(c) &= \int_c^{\infty} p(x|\omega_S))dx - \int_c^{\infty} p(x|\omega_A))dx \\ \frac{dJ}{dc} &= p_S(x) - p_A(x) = 0 \\ p_S(x) &= p_A(x) \end{aligned} \tag{4.6}$$

which means that the optimal *cut-off* under the Youden criterion corresponds to the point where the distributions of both populations intersect, as shown in Fig.4.7.

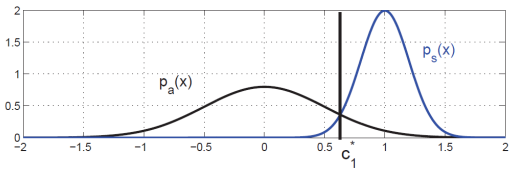


Figure 4.7: Representation of optimal cut-off with the Youden index, occurring in the interception of probability distribution functions.

Once again, the presented results only consider equal weight for the classification of a true positive and a false positive. If one considers that the relative value of this two classifications is different as, for example, selecting a wider portion of the symptomatic population (True Positives) can be more important over the misclassification of asymptomatic patients as symptomatic (False Positives), we must include a weighting variable. Considering λ as the referred variable for Youden's index calculation:

$$J(c) = max\{\lambda * Sensitivity(c) + (1-\lambda)Specificity(c) - 1\} \tag{4.7}$$

$$\begin{aligned} \frac{d}{d(c)}[\lambda \times \int_c^{\infty} p(x|\omega_S)dx + (1-\lambda)\int_c^{\infty} p(x|\omega_A)dx - 1] = 0 \\ \lambda \times p_S(x) - (1-\lambda)p_A(x) = 0 \\ p_S(x) = \frac{1-\lambda}{\lambda} \times p_A(x) \end{aligned} \tag{4.8}$$

4.3.3 Conclusions

From a distribution point of view the first criterion, DDIC involves the cumulative distribution functions while Youden's interpretation involves the density functions associated with both populations. These result in two different graphical interpretations. DDIC is the intersection of the cumulative distribution $C_S(x)$, with $1 - C_A(x)$. Youden's index is graphically interpreted as the intersection of symptomatic population distribution function with the asymptomatic distribution function. In population selection, the inclusion of different weight values λ can be interpreted as a wider, or narrower, selection of the symptomatic population, resulting in bigger or smaller values of Sensitivity and Specificity. Like this, considering a scale of 0 to 1 for λ, it represents an adjustment that can be made to the

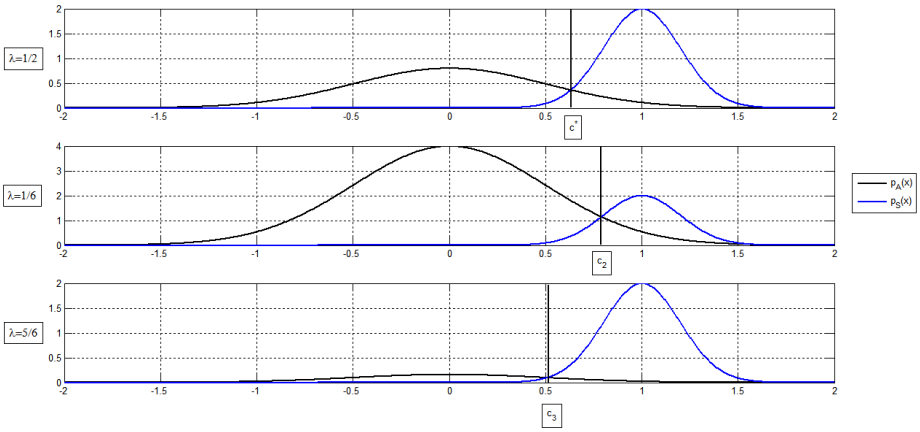


Figure 4.8: Representation of optimal cut-off points (c^*, c_2 and c_3) with Youden's Index, in the probabilistic distribution space for different λ weights.

initial criterion, representing a wider and less demanding selection of TP, lower Sensitivity, for values of λ under 0.5. Values of λ from 0.6 to 1 will represent a narrower selection of the symptomatic population (resulting in lower Specificity). When applying these thoughts to the endarterectomy situation, one would want to have values of λ higher than 0.5, for situations where less resources (human, economical or even logistical) are available. The opposite is also true, indicating with values of λ under 0.5 more patients to surgical treatment.

4.4 ROC Geometrical Approach

ROC curves are used in medicine as a way to analyse the accuracy of diagnostic tests. This allows the determination of the cut-off value for distinguishing between positive and negative test results. Diagnostic testing is almost always a tradeoff between sensitivity and specificity. ROC curves provide a graphic representation of this tradeoff [73].

Since both Sensitivity, $Sens(c)$, and Specificity, $Spec(c)$, depend on the cut-off parameter, the ROC curve can be defined as the following parametric curve, $s(c) : R \rightarrow R^2$, where $s(c) = (\underbrace{1 - Spec(c)}_{x(c)}, \underbrace{Sens(c)}_{y(c)})$. We plot a point representing these rates on a two dimensional graph. The graphical representation of these sensitivity/specificity pairs, when the densities are fixed but the cut-off c is changed, represent the ROC curve.

Figure 4.9 presents four points of analysis. Together, these points represent extreme situations of ROC analysis, gathering also the best and worst case scenarios. Point a) is the best possible result. It represents a test with perfect discrimination with a ROC curve that passes trough the upper left corner. A curve that passes through point c) misses all classifications. It represents a classifier that indicates a healthy patient as diseased, and a diseased patient as healthy. Point b) represents a classification of all individuals as symptomatic, regardless of score. Finally, point d) represents a classification of all patients as asymptomatic, regardless of score. Therefore, the closer the ROC curve is to the upper left corner, the higher is the overall accuracy of the test [55]. The problem under analysis is about Sensitivity/Specificity values between 0 and 1, that result in the representation of

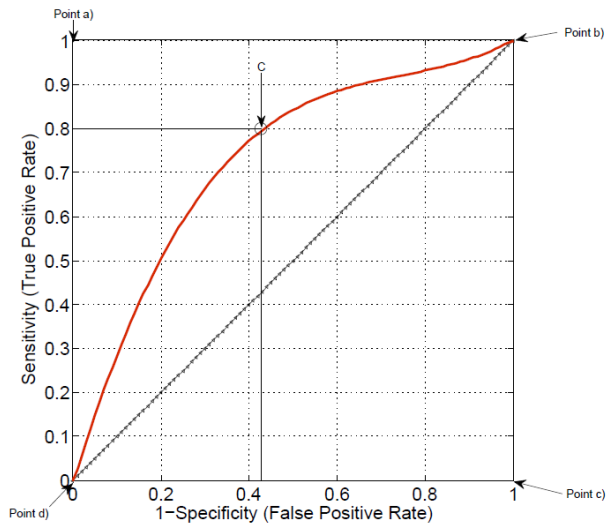


Figure 4.9: Exemplificative ROC curve with reference points.

a curve which demands further evaluation *criteria* for the selection of the appropriate cut-off value. Criteria for the computation of an optimal cut-off value are described next.

4.4.1 *Descending Diagonal Intersection Criterion* (DDIC)

From the ROC perspective, this criteria sets the optimal cut-off in the interception point between the ROC curve and the descending diagonal. This criterion may be formulated as

$$TPR = 1 - FPR \tag{4.9}$$

or using equations 4.1

$$\begin{aligned} \int_c^\infty p(x|\omega_S)dx &= 1 - \int_c^\infty p(x|\omega_A)dx \Leftrightarrow \\ &\Leftrightarrow \end{aligned} \tag{4.10}$$

The interception of the ROC curve with the line at 90 degrees to the no-discrimination line is considered as an heuristic method to investigate the cut-off providing the best discriminative power of the test (or predictive method).

The considered results have not taken into account the possibility of weighting differently the TPR and the FPR. In general medical applications, the cost associated with TPR is different from FPR, hence a weighting them differently is a useful feature. Accordingly, let us consider the cost variable λ in our criterion, and expand equation 4.2, such that:

$$\begin{aligned} \lambda \times TPR &+ (1-\lambda)FPR = \lambda \\ TPR &= 1 - \frac{1-\lambda}{\lambda} \times FPR \end{aligned} \tag{4.11}$$

For easier interpretation, the presented calculations provide a direct graphical and geometrical analysis of the interception line, which allows the selection of the cut-off. Figure 4.10 represents the behaviour of interception lines with different λ values.

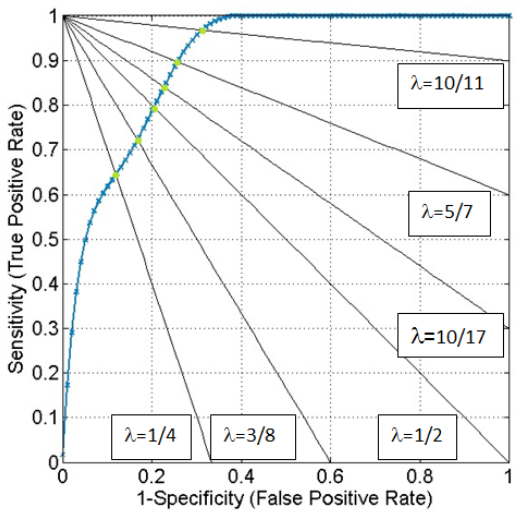


Figure 4.10: Representation of different interception lines weighted by λ for the DDIC.

So, it is easy to understand that weighting the relative importance of TPR over the FPR will, as predicted, result in different interception lines with the ROC curve. The correspondent behavior is represented in Figure 4.8.

4.4.2 *Youden Criterion* (YC)

From a geometrical point of view, this criterion maximizes the vertical distance from the ROC curve to the non-discriminative diagonal. The optimal c^* is computed by finding the stationary point of $J(c)$ with respect to c, $\frac{dJ(c)}{dc} = 0$ which leads to

$$\frac{dTPR(c)}{dc} = \frac{dFPR(c)}{dc} \tag{4.12}$$

or

$$\frac{dTPR}{dFPR}(c) = 1 \tag{4.13}$$

This means that the tangent to the ROC graph at the optimal cut-off, under the Youden criterion, has an unitary slope.

Once again, in order to consider adjustments to cut-off selection, λ is considered in the criterion as a weighting factor. Eq. 4.8 can be written as:

$$\frac{d}{dc}\frac{TPR(c)}{FPR(c)} = \frac{1-\lambda}{\lambda} \tag{4.14}$$

Figure 4.11 is the graphical representation of the result presented by Eq. 4.14. For different relative values of TPR and FPR, Youdens's consideration for cut-off selection will behave according to different slopes for the tangent to the cut-off point on the ROC curve.

4.4.3 Conclusions

The optimal cut-off under both criteria is different. In geometrical terms the DDIC optimal cut-off, c^*, is obtained by intersecting the ROC curve with the descendant diagonal while in the Youden cri-

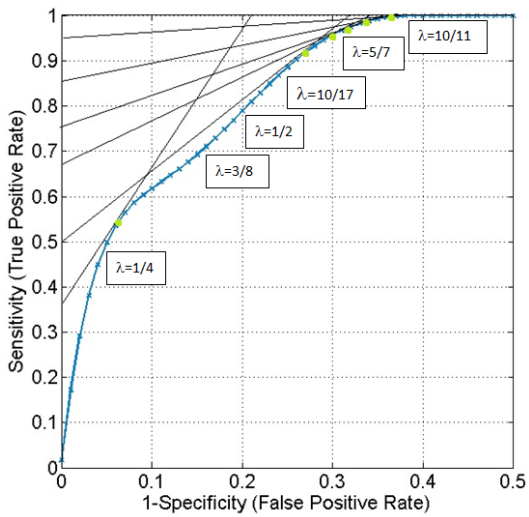


Figure 4.11: Representation of different interception lines weighted by λ for the Youden Index.

terion, the optimal cut-off occurs when the tangent to the ROC curve is unitary. When considering different weights for λ DDIC will select the cut-off value where the ROC curve intersects the descending line with negative slope indicated by $y = 1 - \frac{1-\lambda}{\lambda}x$. In the case of Youden's index, the line tangent to the optimal cut-off point in the ROC curve is given by $y = \frac{1-\lambda}{\lambda}x$. Interpretations made for the probabilistic approach are also valid for the ROC approach. We now have the possibility of acknowledge them graphically. In population selection, the inclusion of different weight values λ can be interpreted as a wider, or narrower, selection of the symptomatic population, resulting in bigger or smaller values of TP fraction. Like this, λ represents an adjustment that can be made to the initial criterion. A narrower and less demanding selection of TP is given by smaller values of λ. Bigger values of λ will represent a wider selection of the symptomatic population (resulting in more TP). When applying these thoughts to the endarterectomy situation, one would want to have bigger values of λ for situations where less resources (human, economical or even logistical) are available. The opposite is also true, allowing with lower values of λ more patients to be submited to surgery. Statistically, it can be contradictory as more FP subjects will be selected for surgery but, on the other hand, we assure a wider selection of the symptomatic population. Like this, further work shall be presented in order to understand how this parameter would result as a cost function.

4.5 Considerations for Carotid Endarterectomy

For the present analysis, we do not intend to have a complete description of all economic aspects related to endarterectomy or building an all inclusive cost estimate of the procedures, follow-up clinic visits and diagnosis. Our goal is to have a general perspective of its associated diagnostic costs, procedural costs and effects allowing to support a better interpretation of the ROC curve and consequent indication, or not, of the patient to surgery. For the exposed, we gathered the information presented in the literature review chapter (Chapter 3) and adapt it to our particular study of complementing the ROC analysis for carotid atherosclerosis diagnosis. Figure 4.12 represents the analysis

that our methodology intends to replicate.

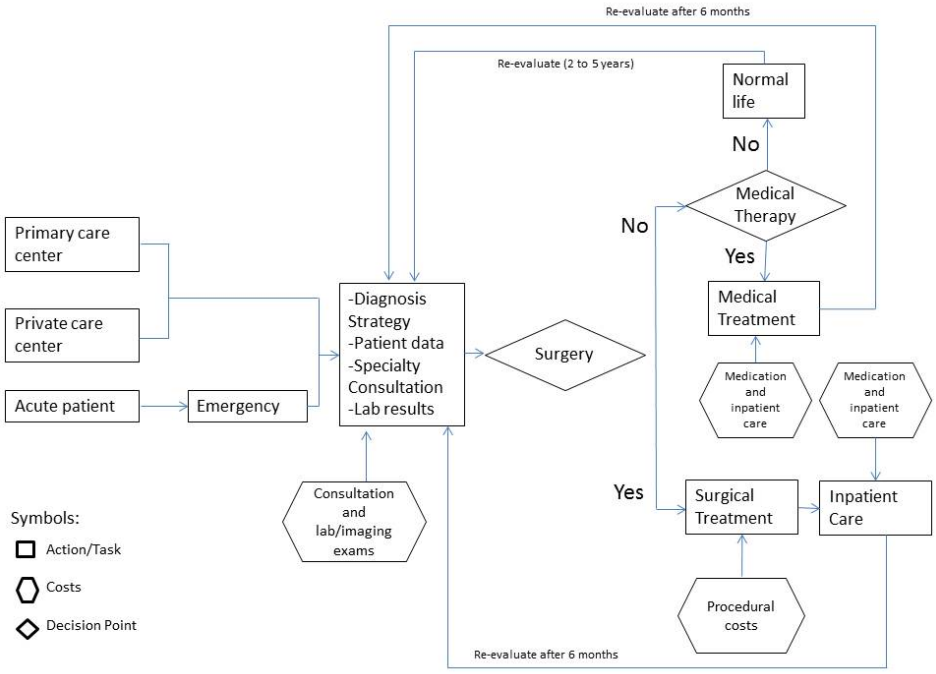


Figure 4.12: Workflow enhancing the decision making process for operating, or not, a carotid atherosclerosis stenosis patient based on the diagnosis evaluation.

This workflow represents the inclusion of patient data as part of the decision process of submitting the patient to surgery, with the intent of better informing the physician. The costs considered in the model are divided in three types: Consultation and lab/imaging exams, Procedural costs and Medication and inpatient care. For a Portuguese private care center, the costs considered for the consultation and lab/imaging exams are approximately 1000€ and 7500€ is the approximate value for the procedural costs of endarterectomy and inpatient care. The total average cost of an endarterectomy is 8500€. These cost data were collected in the private health care provider ICVL. For the cases of the patients that are not submitted to surgery, the total costs that will be considered are 1000€ for the diagnosis and approximately 10€ in medication. Both treatments involve common fixed costs of re-evaluation diagnosis every six months (ultrasound imaging) and every day medication, of approximately 250€ per year, which will be considered for the expected life costs of each treatment alternative. It also important to define a threshold to the value of ICER to consider a treatment alternative cost-effective when compared to other. The common threshold considered in the United Kingdom, proposed by National Institute for Health and Clinical Excellence (NICE), is £30000 [74]. Thus, any health intervention which has an incremental cost of more than £30,000 per additional QALY gained is likely to be rejected and any intervention which has an incremental cost of less than or equal to £30,000 per extra QALY gained is likely to be accepted as cost-effective. Taking into account an approximate value in Euro, we will consider 35000€ as the threshold for ICER for the present context.

The considered prevalence of the carotid atherosclerosis disease, for the Portuguese context of a private health provider with patients from other health specialties like neurology and cardiology, is

31.8%, as already referred in Subsection 3.2.4. This will be important for the calculation of positive and negative predictive values.

We will incorporate the age (and gender) influence in the decision making process in terms of utility. Table 4.1 from the study presented by Mahoney et al. [1], represents the utility values that shall be considered for the present analysis. Nevertheless, the average life expectancy in Portugal, with values updated in the 30th of May (2012) by INE (Instituto Nacional de Estatística) and PORData (Base de dados de Portugal Contemporâneo), is 76.4 years for men and 82.3 years for women [75] and shall be considered.

Table 4.1: Summary of Assumptions and Data Sources for Long-Term Cost and Life Expectancy Projections for a 72-year-old subject [1].

	Annual cost	Life expectancy	Utility	QALYs	Lost life years	Lost QALYs
Males						
No event	$5817	8.22	0.841	6.91	0	0
MI	$10176	3,85	0,737	2,84	4,37	4,07
Major stroke	$18515	5,28	0,436	2,3	2,94	4,61
MI + major stroke	$18515	3,85	0,436	1,68	4,37	5,23
Minor stroke	$5817	8,22	0,729	5,99	0	0,92
Females						
No event	$5817	9,34	0,833	7,78	0	0
MI	$10176	4,22	0,733	3,09	5,12	4,69
Major stroke	$18515	5,73	0,433	2,48	3,61	5,3
MI + major stroke	$18515	4,22	0,433	1,83	5,12	5,95
Minor stroke	$5817	9,34	0,725	6,77	0	1,01

4.5.1 Conclusions

With the presented points of analysis, this work will allow to complete the decision making process with a more informed basis, together with Enhanced Activity Index. The tool presented in the next chapter will use the economic information presented previously and enables the physician to gather information about the patient, the outcomes of the selected treatment and the ICER of each decision.

5

Application of the proposed Methodology

Contents

ï»¿ *The present chapter will introduce a graphical user interface that gathers all the concepts and information already presented. The GUI was developed in the software Matlab and enables several tools for the physician to perform a more informed decision. The inputs needed for the software are presented, as well as, the output results.*

5.1 Computational Implementation

For the presented model, the intent was to include information about the patient and economical aspects together with Enhanced activity index, which indicates the plaque activity provided by the classification framework. Like this, not only the diagnosis information would be taken into account, but also economical. A correct interpretation of the results will enable to decide wether endarterectomy is the right treatment to a specific patient, in a specific time frame.

It was important to take into account patient age, wether he was symptomatic or asymptomatic and its gender. With this three aspects, one can associate new information to the decision making process. This information includes the possibility of understanding the costs associated with both endarterectomy, and medical therapy as alternative, the life expectancy of the patient and the quality-adjusted life years for each alternative. We also present the “no treatment alternative”, in order to better assess the increment in life expectancy that both endarterectomy and medical therapy provide.

For an adaptive ROC analysis, the GUI should present a ROC curve representative of the Portuguese Private Health Providers reality. The available dataset contains 146 plaques, from a cross-sectional study of 99 patients (75 males and 24 females with a mean age of 68 years (41-88) acquired at Instituto Cardiovascular de Lisboa and Department of Vascular Surgery, Hospital de Santa Maria, Lisbon. They result from the diagnosis of carotid atherosclerosis and the ground truth of this database is that 44 were symptomatic plaques and the remaining 102 were asymptomatic [2].

In this part of the GUI, there is the interest of assessing the best cut-off point, which determines the point representative of the decision change, between operating the patient or not. Its sensitivity, specificity, accuracy, positive predictive value and negative predictive value are also important to understand the relevance of the decision made.

Like this, using the software Matlab, from MathWorks, Inc. (1984-2012) , Version R2012a, we were able to create a graphical user interface (GUI) to perform the analysis. Figure 5.1 presents the interface created.

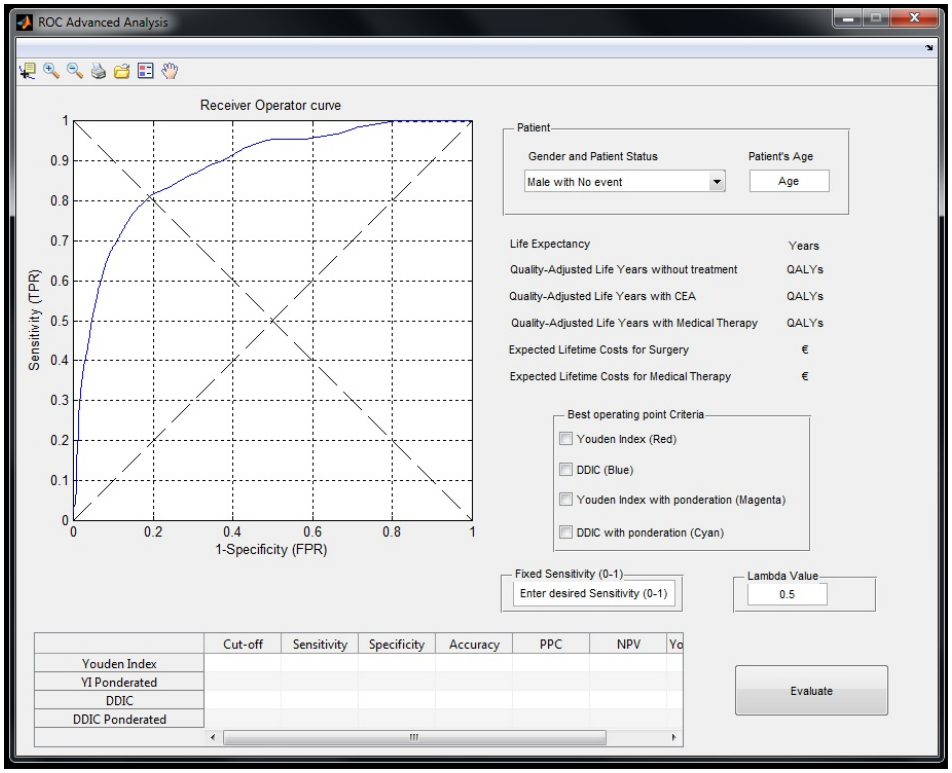


Figure 5.1: Image of the GUI created in Matlab.

5.2 Instructions and available tools

The structure of the interface is now explained, dividing the subject by the ROC curve analysis and the economic information.

For the economic analysis, the user will only need the age, gender and patient status (asymptomatic - no event, or, symptomatic). This last input is made in a pop-up menu that presents the following alternatives:

- Male with No event
- Male with Myocardial Infarction
- Male with Major stroke
- Male with MI + major stroke
- Male with Minor stroke
- Female with No event
- Female with Myocardial Infarction
- Female with Major stroke
- Female with MI + major stroke
- Female with Minor stroke

Each of this options has an utility associated and enables the presentation of life expectancy for the patient, QALYs and estimated costs. All these results are presented to the possibility of endarterectomy and to medical therapy in form of a static text. The GUI is supposed to refresh the results, each

time one selects the patient status. Hence, it is advised for the user to firstly fill the patient's age, selecting the patient's status lastly.

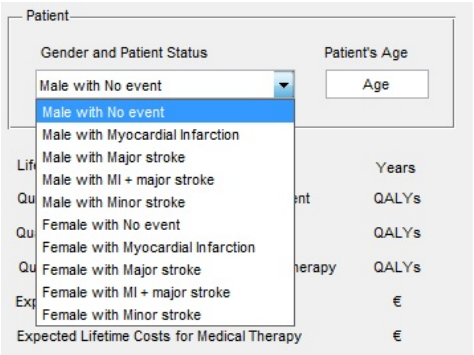


Figure 5.2: Image of the pop-up menu for Gender and Patient Status Selection.

When the referred fields are completed, a pop-up window will be shown to indicate QALY and ICER associated to patient information and health condition. This calculations were made based in the utilities and effects presented in Section 4.5. The costs will include pre-treatment expenses (imaging, lab tests and consultation costs) and procedural costs (endarterectomy, hospitalization and inpatient care).

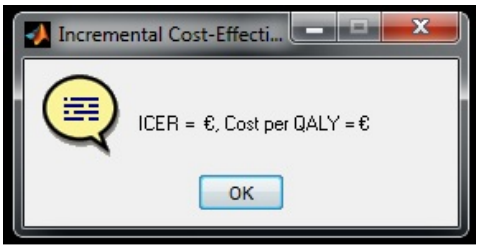


Figure 5.3: Image of the pop-up window for QALY and ICER presentation, when age and patient status are indicated.

For the advanced ROC analysis, the user shall select the *criteria* to assess the optimal cut-off point. Four possibilities are available:

- Youden's Index
- Descending Diagonal Criterion
- Youden Index with weighing
- Descending Diagonal Criterion with weighing.

This selection, made in check boxes on the Best Operating Point Criteria block, will represent a dot in the ROC curve in red, blue, magenta and cyan, respectively representing the best operating point for the selected criteria. The referred weighing is made in the field Lambda Value, that represents the factor of weighing differently sensitivity and specificity, as already explained in Chapter 4.

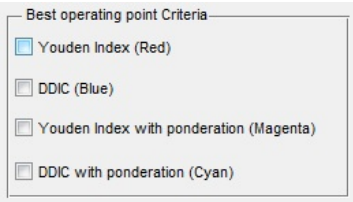


Figure 5.4: Image of the check box menu for cut-off selection criteria.

It is also available the possibility of drawing a line representing a fixed sensitivity, which presents also the respective cut-off point (interception of the ROC curve with the Fixed Sensitivity line). The results will be presented in a table, when the button Evaluate is pressed. Each time the parameters are changed and the evaluate button is pressed, new results on the table are presented and the dots on the ROC curve for the criteria will be repositioned.

The toolbox in the top of the GUI's window also includes some other tools. It contains a data cursor, to navigate through the ROC curve, assessing the TPR (Sensitivity - yy axle) and FPR (1-Specificity - xx axle) values. Also zoom and pan tools are available, in order to select a specific region of the curve. Figure 5.5 is illustrative.

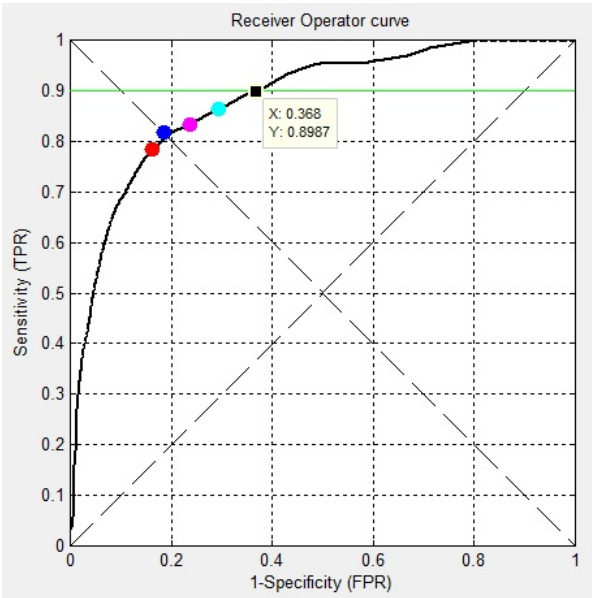


Figure 5.5: Image of the available ROC tools.

With the presented interface, the physician can support the decision in hand with statistical data. The relevance of ones decision, will be sustained by sensitivity and specificity of a representative data base, as well as, by the accuracy, positive predictive value and negative predictive value of the optimal operating point. The group of information gathered in the GUI of advanced ROC analysis, together with EAI (or Degree of stenosis, for example) will constitute a useful tool in the decision making process for endarterectomy.

6

Results and Discussion

Contents

In this chapter, hypothetical patient examples are presented and analysed. The subjects in question enable the possibility of discussing the output results of ROC advanced analysis Graphical User Interface (GUI), presented previously. It is made an attempt to illustrate common possibilities of a patient condition and also, other aspects that may represent added value for the physician, in terms of decision support.

6.1 Results

Nowadays, the selection of patients to endarterectomy is made based on diagnosis information together with the experience/knowledge of the physician. The degree of stenosis and the associated risk of atherosclerosis to the patient is the index considered. We pretend to assess the Incremental Cost-Effectiveness Ratio, base on the costs (C) and Effects (E), measured in QALYs for our model, together with the advanced ROC analysis. It is important to understand interpreting the information is simple and results in a suggestion of the best treatment option for the patient. It is usual to consider approximately 35000€ per QALY threshold, when considering an alternative cost-effective compared to another.

6.1.1 Example of an asymptomatic male patient

It is presented now an hypothetical 65-year-old asymptomatic male patient with high degree of stenosis (superior to 70%) or equivalent EAI. From the exposed in the bibliographic review, this type of patient is not consensual about the benefit of surgical treatment. From Figure 6.1 it is possible to observe that the difference in QALYs from the endarterectomy to the medical therapy is minimal and the costs differential is high.

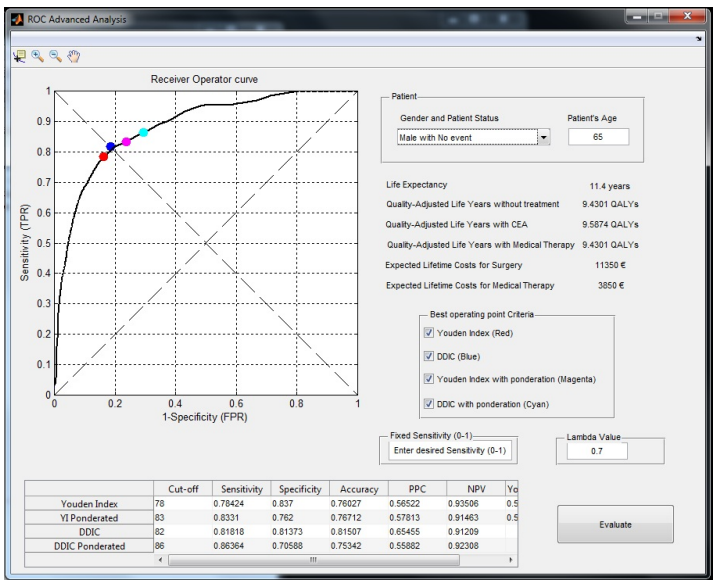


Figure 6.1: Results for a 65-year-old male asymptomatic patient.

This results represent an ICER of approximately 48000€ and surgery is considered cost-effective when compared to medical treatment.

$$ICER = \frac{C(Surgery) - C(MedicalTherapy)}{E(Surgery) - E(MedicalTherapy)} = 47679.6 \tag{6.1}$$

From the ROC analysis, if the patient has an EAI superior to 78 (0-100), surgery is the recommended treatment (by Youden's index), as the economic information presented above already suggested. If the ROC analysis is performed considering that asymptomatic patients have higher associated risk in surgery, attributing a higher weighing to Sensitivity (using a Lambda value of 0.6) will ensure that only patients with higher EAI (82 or superior) will be indicated to surgery.

Lets now evaluate a situation where a patient is older (72 and 73 years old) and also asymptomatic.

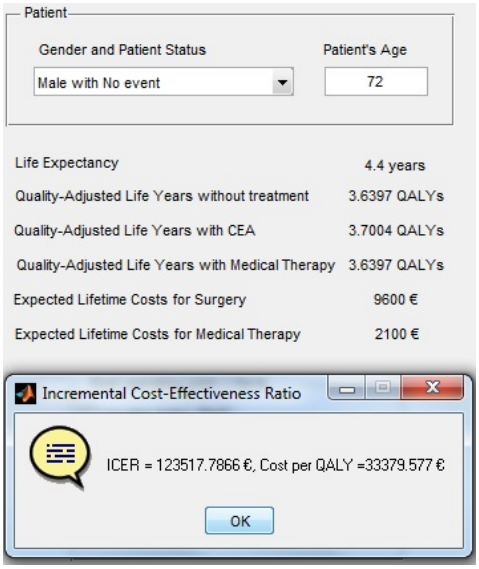


Figure 6.2: Results for a 72-year-old male asymptomatic patient.

Despite the high ICER, Figure 6.2 shows that surgery is cost-effective.

Figure 6.3 shows that the difference in QALYs is even lower.

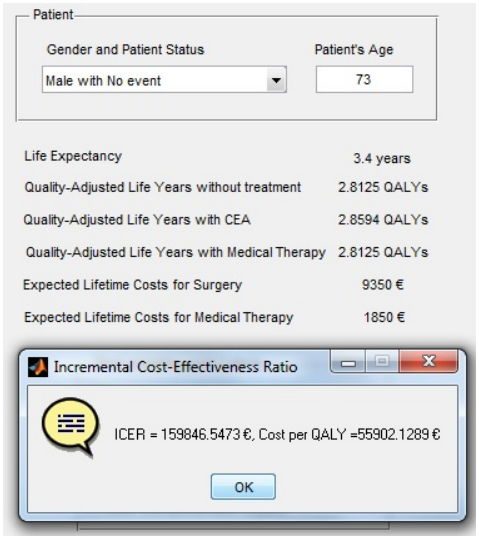


Figure 6.3: Results for a 73-year-old male asymptomatic patient.

In this case, as the ICER is 159846.55€ with a cost per QALY of 55902.13€. This situation allows

to interpret that surgery in an asymptomatic patient with severe stenosis is not cost effective if the patient is 73 years or older, as it will represent a cost per QALY superior to the threshold of 35000€.

6.1.2 Example of a symptomatic male patient

It is now analysed the situation of symptomatic male patients, victims of myocardial infarction. Figures 6.4 and 6.5 show, as expected, that patients with this characteristics are indicated to surgery, with a ICER between 56045.47€ and 107939.42€ and a cost per QALY between 5909.85€ and 20449.27€. It is important to remind that these results take into account the life expectancy of 76.4 years to male patients.

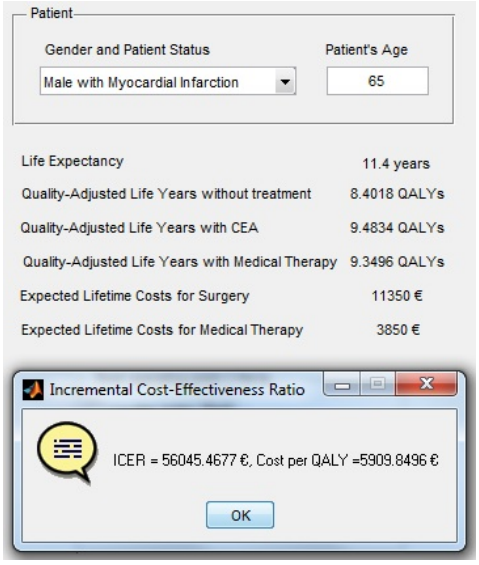


Figure 6.4: Results for a 65-year-old male symptomatic patient.

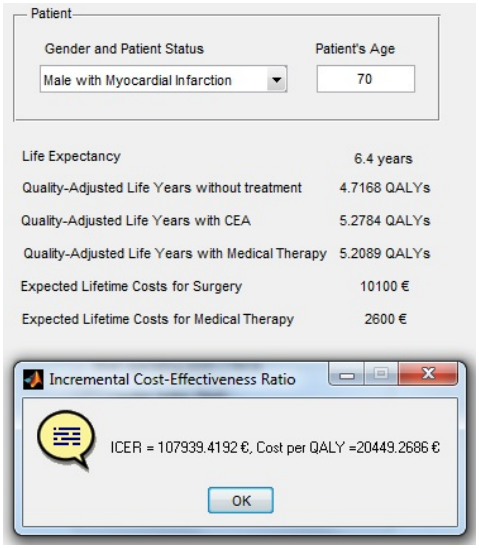


Figure 6.5: Results for a 70-year-old male symptomatic patient.

On the contrary, patients above 71 years old with a myocardial infarction plus major stroke occurrence, will represent a cost per QALY higher then 35000€, being medical therapy the most adequate

treatment, as shown in Figure 6.6.

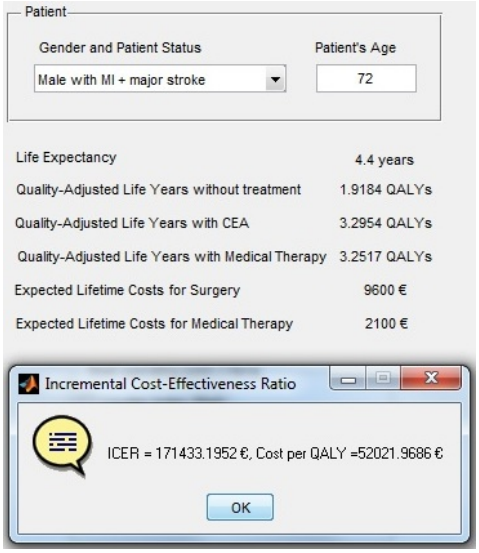


Figure 6.6: Results for a 71-year-old male symptomatic patient.

Together with ROC analysis shown in Figure 6.7, it is demonstrated that using Youden's index or DDIC, the cut-off will be of 78 and 82 respectively. For this, regarding that the symptomatic situation enhances endarterectomy as the most appropriate treatment, lower cut-off values (lambda of 0.4) will be adequate. This represents higher specificity and lower sensitivity values for the optimal cut-off, indicating a wider selection of patients for surgical treatment. Every symptomatic male patient with an EAI equal, or superior, to 69 (by Youden's index - magenta) or 77 (by DDIC critetion - cyan) will be indicated to surgery.

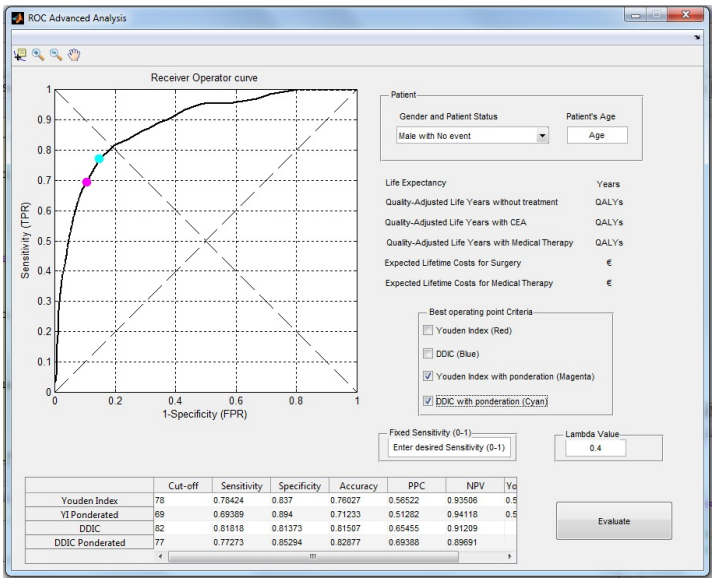


Figure 6.7: Results for a male symptomatic patient. Youden's index optimal cut-off - magenta. DDIC optimal cut-off - cyan.

6.1.3 Example of a female patient

In Table 4.1 it is possible to see that the utilities used to quantify each health state for women, are similar. The main difference is in life expectancy, which is 82.3 years for women. Like this, it is expected that cost per QALY values, for the ages studied before in men, will be lower. Nevertheless, differences in QALYs between surgical treatment and medical therapy is low, leading to high ICER values.

ICER values, for a 65-year-old patient go from 180635.84€ (asymptomatic) to 190471.79€. This values are extremely high, when compared to ICER values in men of this age. These ICER values suggest that surgery is not cost-effective when compared to medical therapy. In this case, a ROC analysis with higher weighing of sensitivity will narrow patient indication to surgery. An evaluation like this is coherent with the low increment in QALY compared to medical therapy. The results table for optimal cut-off criteria shown in Figure 6.8, are representative of a cut-off selection appropriate to this situation, where only female patients with an EAI of 83 or higher (for Youden's index - magenta) are indicated for endarterectomy.

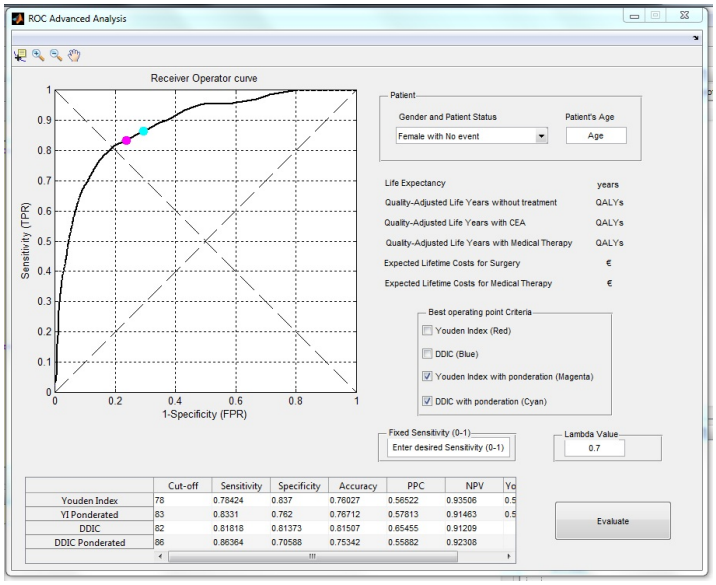


Figure 6.8: Results for a female patient. Youden's index optimal cut-off - magenta. DDIC optimal cut-off - cyan.

6.2 Discussion of the results

The results presented by the created tool corroborate literature references about the cost-effectiveness of endarterectomy in patients with asymptomatic carotid artery stenosis [27]. Considering a willingness-to-pay of 35000€ per QALY, male patients older than 72 years old are indicated to medical therapy, instead of endarterectomy. Also, in our consideration, a higher sensitivity for the optimal operating point (with a lambda value of 0.6) is the most indicated. It represents that only patients with higher values of EAI (or Degree of stenosis) will be selected to surgery, avoiding a riskier treatment solution with higher costs to patients with lower EAI (between 70 and 81).

In the case of symptomatic male patients, ROC analysis has a preponderant part in the decision

making process. Despite the indication of high cost per QALY in patients older than 72 years old, the risk of other symptomatic occurrences is high and surgical treatment should be considered. The adjustment made to find the optimal cut-off for this situation, by using a lambda of 0.4 will include a wider spectrum of symptomatic patients, with EAI of 69 or higher.

Female patients represent high ICER values for the ages analysed (65 to 70, which represent the median age of endarterectomy patients in Europe). Like this, higher lambda values will compensate this fact, by determining higher cut-off values, as endarterectomy does not constitute a better alternative than medical therapy.

The difference in cut-off selection represents different values in sensitivity and specificity. When the lambda value assigns equal importance to sensitivity and specificity, both criteria have similar results, with differences around 2%. If we assign different weighing (with lambda values different of 0.5), the differences go from 2% to 10%. It is important to highlight that DDIC has, for the examples presented above, higher accuracy and, generally, Sensitivity and Specificity.

The results presented could be improved in terms of specifying and detailing all the relevant costs associated to endarterectomy. To present a full economic analysis for the Portuguese reality, would be useful to register direct and indirect costs. The collection of cost data during a period of 12 months, for example, would enable an analysis considering seasoning and resource availability during the year. This type of review is interesting to understand the fluctuations existent in periods like holidays and their impact in the costs of the procedure.

Also, when analysing patients younger than 65 years old, which is the retirement age, no adjustment was made for loss of productivity. The tool provided only considers direct costs associated to diagnosis and treatment.

Another point of interest would be to relate age with differences detected in costs. There is evidence in the literature [67] that indicates a direct relation between age and the length of hospitalization, having direct influence in the total cost of the treatment.

6.3 Summary

With the presented results it is demonstrated that a correct analysis of a ROC curve, demonstrative of the carotid atherosclerosis reality, together with economic information creates an informed decision making process. In the hypothetical examples created, it was shown that some situations demand a correct adaptation of the cut-off value for patient selection to endarterectomy, according to the available information about the patient and the expected effect that surgery will provide in terms of quality of life.

7

Conclusions and Further work

This thesis intended to complete the information implied in EAI with economic factors, to better assess the decision making process of indicating a patient to endarterectomy.

A presentation of the context about carotid atherosclerosis and its possible treatments in made in Chapter 2. It is also introduced the fundamentals of ROC curve analysis and economic evaluations for endarterectomy. The latter are important to support the decision making process for endarterectomy in a wider perspective, complementing the medical aspects with economic and other related information.

Based on a literature review, presented in Chapter 3, about ROC curves and economic evaluations for endarterectomy, a broader tool was proposed to enable the analysis of factors like age, gender, expected costs and effects of surgery to the patient together with the already existent index. This tool, introduced in Chapter 5, was created using the software Matlab and, by the use of Receiver Operating Curves, it was intended to understand the behaviour of an existing data base of 146 atherosclerotic plaques, demonstrative of carotid atherosclerosis population that resorted the Portuguese private health care provider ICVL. Using adequate criteria that was analysed in Chapter 4, it is suggested an optimal cut-off point for patient indication to surgery, based on their EAI (or Degree of Stenosis (DS)). The complement of this information presents the associated effects of endarterectomy, in terms of Quality-Adjusted Life Years, and its respective Incremental Cost-Effectiveness Ratio when compared to medical therapy, taking into account patient age, gender and condition.

The objectives outlined for the thesis were achieved and when having a previous diagnosis and respective atherosclerosis index, like EAI, the physician is able to assess if the score attributed by the index determines wether the best treatment available is endarterectomy, comparing to medical therapy. If the score is higher than the optimal cut-off presented by the ROC analysis, the physician can understand if endarterectomy is cost-effective and determine if it is the most adequate treatment for the patient. The results presented in Chapter 6 corroborate previous indications of the bibliography, even in asymptomatic patients, where it is not consensual the benefit of carotid endarterectomy. It is plausible to affirm that the analysis created is consistent and useful for clinical practice assistance in the decision making process.

Nevertheless, it would be interesting to incorporate both the EAI and the economic information together in a global index. To present a full economic analysis for the Portuguese reality, would be useful to register direct and indirect costs and conclude the effectiveness of endarterectomy. The collection of cost data during a period of 12 months, for example, would enable an analysis considering seasoning and resource availability during the year. This type of review is interesting to understand the fluctuations existent in periods like holidays and their impact in the costs of the procedure. Also, to divide the outcomes in terms of QALY by age groups would allow an adjustment in terms of questions like productivity and associated loss to society. The relation between age and the length of hospitalization has direct influence in the total cost of the treatment, being the association of age to the costs a point of interest.

The combination of the created tool with the existing software for EAI calculation, would simplify the decision making process. The inclusion of its usage as common practice in health care providers

should be tested and further studies including cost-effectiveness analysis of more treatment possibilities, like CAS, would represent an additional step. In terms of value added to the scientific community, we consider that the present thesis is the initial step to suggest a broader software for carotid atherosclerosis diagnosis.

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A

Matlab code for the GUI

Here are presented the main functions of the GUI interface. The Matlab code presented does not include the functions common to every GUI tool created. Like this, it is possible to assess the principals and behaviour of the functions presented in Chapter 5.

```
— Executes just before GUI of ROCeai is made visible.
function ROCeai_OpeningFcn(hObject, eventdata, handles, varargin)

plot([0,1],[0,1],'–k',[0,1],[1,0],'–k'); diagonal plots
hold on;
title('Receiver Operator curve');
xlabel('1-Specificity (FPR)');
ylabel('Sensitivity (TPR)');
grid on; axis square; axis([0 1 0 1]);

Function that draws the fixed Sensitivity line in the ROC plot:
function FixedSens_Callback(hObject, eventdata, handles)
valor_sens = get(hObject,'Value');
string_sens = get(hObject,'String');
recta = str2num(string_sens); y=recta; x= 0:0.01:1;
handles.plot_fixedSens = plot([0,1],[recta,recta],'g');
fixedSens = str2num(get(handles.FixedSens,'String'));
```

Function that calculates the Fixed Sensitivity Cut-off

```
inc=1;
prox_zero=inf;
fixed_sensitivity=0;
while inc<length(handles.Yi)
if abs(fixedSens-handles.Yi(inc))<prox_zero,
prox_zero=abs(fixedSens-handles.Yi(inc));
fixed_sensitivity=inc;
end
inc=inc+1;
end
handles.fixedSens_readcut=round(handles.Yi(fixed_sensitivity)*
100/max(handles.Yi));
set(handles.st_fixed_sens,'String',
(['Cut-off =' num2str(handles.fixedSens_readcut)]);
```

Function that attributes the utility values accordingly to patient gender and status

```
handles.age = str2num(get(handles.Age,'String'));
switch get(hObject,'Value')
case 1
handles.current_data = 76.4-handles.age;
if handles.current_data<0
msgbox('Life Expectancy in null.
Expected costs shall not be considered','Warning','warn')
end
handles.utility_notreatment=handles.current_data*0.8272;
handles.utility=handles.current_data*0.841;
handles.utility_therapy=handles.current_data*0.8272;
handles.costs_surgery=8500+250*handles.current_data;
handles.costs_therapy=1000+250*handles.current_data;
case 2
handles.current_data = 76.4-handles.age;
if handles.current_data<0
msgbox('Life Expectancy in null.
Expected costs shall not be considered','Warning','warn')
end
handles.utility_notreatment=handles.current_data*0.737;
handles.utility=(handles.current_data-1)*0.841+0.737;
handles.utility_therapy=(handles.current_data-1)*(0.9847*0.841)+0.737;
handles.costs_surgery=8500+250*handles.current_data;
handles.costs_therapy=1000+250*handles.current_data;
case 3
handles.current_data = 76.4-handles.age;
if handles.current_data<0
msgbox('Life Expectancy in null.
Expected costs shall not be considered','Warning','warn')
end
handles.utility_notreatment=handles.current_data*0.436;
handles.utility=(handles.current_data-1)*0.841+0.436;
handles.utility_therapy=(handles.current_data-1)*0.9847*0.841+0.436;
handles.costs_surgery=8500+250*handles.current_data;
handles.costs_therapy=1000+250*handles.current_data;
case 4
handles.current_data = 76.4-handles.age;
if handles.current_data<0
msgbox('Life Expectancy in null.
Expected costs shall not be considered','Warning','warn')
end
handles.utility_notreatment=handles.current_data*0.436;
handles.utility=(handles.current_data-1)*0.841+0.436;
handles.utility_therapy=(handles.current_data-1)*0.9847*0.841+0.436;
handles.costs_surgery=8500+250*handles.current_data;
handles.costs_therapy=1000+250*handles.current_data;
case 5
handles.current_data = 76.4-handles.age;
if handles.current_data<0
msgbox('Life Expectancy in null.
Expected costs shall not be considered','Warning','warn')
end
handles.utility_notreatment=handles.current_data*0.729;
handles.utility=(handles.current_data-1)*0.841+0.729;
handles.utility_therapy=(handles.current_data-1)*0.9847*0.841+0.729;
handles.costs_surgery=8500+250*handles.current_data;
handles.costs_therapy=1000+250*handles.current_data;
case 6
handles.current_data = 82.3-handles.age;
if handles.current_data<0
msgbox('Life Expectancy in null.
Expected costs shall not be considered','Warning','warn')
end
handles.utility_notreatment=handles.current_data*0.8306;
handles.utility=handles.current_data*0.833;
handles.utility_therapy=handles.current_data*0.8306;
handles.costs_surgery=8500+250*handles.current_data;
handles.costs_therapy=1000+250*handles.current_data;
case 7
handles.current_data = 82.3-handles.age;
if handles.current_data<0
msgbox('Life Expectancy in null.
Expected costs shall not be considered','Warning','warn')
end
handles.utility_notreatment=handles.current_data*0.733;
handles.utility=(handles.current_data-1)*0.833+0.733;
handles.utility_therapy=(handles.current_data-1)*0.9971*0.833+0.733;
handles.costs_surgery=8500+250*handles.current_data;
handles.costs_therapy=1000+250*handles.current_data;
case 8
handles.current_data = 82.3-handles.age;
if handles.current_data<0
msgbox('Life Expectancy in null.
Expected costs shall not be considered','Warning','warn')
end
handles.utility_notreatment=handles.current_data*0.433;
handles.utility=(handles.current_data-1)*0.833+0.433;
handles.utility_therapy=(handles.current_data-1)*0.9971*0.833+0.433;
handles.costs_surgery=8500+250*handles.current_data;
handles.costs_therapy=1000+250*handles.current_data;
case 9
handles.current_data = 82.3-handles.age;
if handles.current_data<0
msgbox('Life Expectancy in null.
Expected costs shall not be considered','Warning','warn')
end
handles.utility_notreatment=handles.current_data*0.433;
handles.utility=(handles.current_data-1)*0.833+0.433;
handles.utility_therapy=(handles.current_data-1)*0.9971*0.833+0.433;
handles.costs_surgery=8500+250*handles.current_data;
handles.costs_therapy=1000+250*handles.current_data;
case 10
handles.current_data = 82.3-handles.age;
if handles.current_data<0
msgbox('Life Expectancy in null.
Expected costs shall not be considered','Warning','warn')
end
handles.utility_notreatment=handles.current_data*0.725;
handles.utility=(handles.current_data-1)*0.833+0.725;
handles.utility_therapy=(handles.current_data-1)*0.9971*0.833+0.725;
handles.costs_surgery=8500+250*handles.current_data;
handles.costs_therapy=1000+250*handles.current_data;
end
```

Calculation/Presentation of QALYs, ICER and Costs

```
handles.icer= (handles.costs_surgery-handles.costs_therapy)/
(handles.utility-handles.utility_therapy);
```

```
handles.costperqaly=handles.icer/handles.utility;

    guidata(hObject,handles)

    set(handles.st_life_expectancy,'String',[num2str(handles.current_data)
' years']);
set(handles.st_qalys,'String',[num2str(handles.utility_notreatment)      '
QALYs']);
set(handles.st_cost_surgery,'String',[num2str(handles.costs_surgery) '
€']);
set(handles.st_costs_therapy,'String',[num2str(handles.costs_therapy)
' €']);
set(handles.QALYCEA,'String',[num2str(handles.utility) ' QALYs']);
set(handles.QALYtherapy,'String',[num2str(handles.utility_therapy)      '
QALYs']);
msgbox(['ICER = ' num2str(handles.icer) '
€,Cost per QALY =' num2str(handles.costperqaly) ' €'],
'Incremental Cost-Effectiveness Ratio','help');
handles.age = str2num(get(handles.Age,'String'));
```

ROC curve plotting

```
lambda = str2num(get(handles.lambda,'String'));
load CP.mat;

    if nargin<1, s = 40; end
if nargin < 2, r = 1000; end
out = []; s = 15; r = 1000;
X = 1 - CP.ICVLdavid.EAIprod_App.Specificity;
Y = CP.ICVLdavid.EAIprod_App.Sensitivity;
S = CP.ICVLdavid.EAIprod_App.cutoff;
Xs = smooth(X,s); Ys = smooth(Y,s);
Xi = 0:(1/r):1; handles.Xi=Xi; Yi = spline(Xs,Ys,Xi); handles.Yi=Yi;
handles.roc = plot(handles.ROCcurve,Xi,Yi,'k','LineWidth',2);
```

Fixed Sensitivity

```
    inc=1; prox_zero=inf; fixed_sensitivity=0;
while inc<length(handles.Yi)
if abs(fixedSens-handles.Yi(inc))<prox_zero,
prox_zero=abs(fixedSens-handles.Yi(inc));
fixed_sensitivity=inc;
end
inc=inc+1; end
handles.fixedSens_readcut=round(handles.Yi(fixed_sensitivity)*
100/max(handles.Yi));
set(handles.st_fixed_sens,'String',
([num2str(handles.fixedSens_readcut)]);
```

Youden's index calculation

```
    handles.a=1; handles.i=1; handles.j=1;
handles.auxx=-inf; handles.aux=-inf; handles.minimo=inf;
handles.cut=0; handles.cutt=0;
handles.m=(1-lambda)/lambda;
while handles.i<=length(Yi),
if Yi(handles.i)+(1-Xi(handles.i))-1>handles.aux
handles.aux=Yi(handles.i)+(1-Xi(handles.i))-1;
handles.cut=handles.i;
end
handles.i=handles.i+1; end
handles.readcut=round(Yi(handles.cut)*100/max(Yi));
handles.aux=
CP.ICVLdavid.EAIprod_App.Sensitivity(handles.readcut)+
CP.ICVLdavid.EAIprod_App.Specificity(handles.readcut)-1;

    while handles.j < length(Xi),
if abs(handles.m-(Yi(handles.j+1)-Yi(handles.j))/
(Xi(handles.j+1)-Xi(handles.j)))<handles.minimo
handles.minimo = abs(handles.m-(Yi(handles.j+1)-
Yi(handles.j))/(Xi(handles.j+1)-Xi(handles.j)));
handles.cutt = handles.j; end
handles.j=handles.j+1; end
handles.readcutt=round(Yi(handles.cutt)*100/max(Yi));
handles.auxx=
CP.ICVLdavid.EAIprod_App.Sensitivity(handles.readcutt)+
CP.ICVLdavid.EAIprod_App.Specificity(handles.readcutt)-1;
```

Creation of Youden results Table

```
    handles.mat1,1 = num2str(handles.readcut);
handles.mat1,2 = num2str(Yi(handles.cut));
handles.mat1,3 = num2str(1-Xi(handles.cut));
handles.mat1,4 = num2str(CP.ICVLdavid.EAIprod_App.Accuracy(handles.readcut));
handles.mat1,5 = num2str(CP.ICVLdavid.EAIprod_App.PPV(handles.readcut));
handles.mat1,6 = num2str(CP.ICVLdavid.EAIprod_App.NPV(handles.readcut));
handles.mat1,7 = num2str(handles.aux);
handles.mat2,1 = num2str(handles.readcutt);
handles.mat2,2 = num2str(Yi(handles.cutt));
handles.mat2,3 = num2str(1-Xi(handles.cutt));
handles.mat2,4 = num2str(CP.ICVLdavid.EAIprod_App.Accuracy(handles.readcutt));
handles.mat2,5 = num2str(CP.ICVLdavid.EAIprod_App.PPV(handles.readcutt));
handles.mat2,6 = num2str(CP.ICVLdavid.EAIprod_App.NPV(handles.readcutt));
handles.mat2,7 = num2str(handles.auxx);
```

DDIC cut-off calculation

```
    handles.vSens = CP.ICVLdavid.EAIprod_App.Sensitivity;
handles.vSpec = CP.ICVLdavid.EAIprod_App.Specificity;
handles.ddic.Xi=1-handles.vSpec;
handles.v_thrs = CP.ICVLdavid.EAIprod_App.cutoff;
handles.ddic.i=1; handles.ddic.j=1;
handles.ddic.aux=inf; handles.ddic.aux2=inf;
handles.ddic.cut=0; handles.ddic.cutt=0;

    while handles.ddic.i <= length(handles.v_thrs),
if abs(handles.vSens(handles.ddic.i)-handles.vSpec(handles.ddic.i))<
handles.ddic.aux
handles.ddic.aux = abs(handles.vSens(handles.ddic.i)-
handles.vSpec(handles.ddic.i));
handles.ddic.cut = handles.ddic.i;
end
handles.ddic.i=handles.ddic.i+1; end

    handles.ddic.readcut=round(handles.vSens(handles.ddic.cut)*
100/max(handles.vSens));

    while handles.ddic.j <= length(handles.v_thrs),
if abs(lambda*handles.vSens(handles.ddic.j)+
(1-lambda)*(1-handles.vSpec(handles.ddic.j))-lambda)<handles.ddic.aux2,
handles.ddic.aux2 = abs(lambda*handles.vSens(handles.ddic.j)+
(1-lambda)*(1-handles.vSpec(handles.ddic.j))-lambda);
handles.ddic.cutt = handles.ddic.j;
end
handles.ddic.j=handles.ddic.j+1; end

    handles.ddic.readcutt=round(handles.vSens(handles.ddic.cutt)*
100/max(handles.vSens));
```

Creation of DDIC results Table

```
    handles.mat3,1 = num2str(handles.ddic.readcut);
handles.mat3,2 = num2str(handles.vSens(handles.ddic.cut));
handles.mat3,3 = num2str(handles.vSpec(handles.ddic.cut));
handles.mat3,4 = num2str(CP.ICVLdavid.EAIprod_App.Accuracy(handles.ddic.cut));
handles.mat3,5 = num2str(CP.ICVLdavid.EAIprod_App.PPV(handles.ddic.cut));
handles.mat3,6 = num2str(CP.ICVLdavid.EAIprod_App.NPV(handles.ddic.cut));
handles.mat4,1 = num2str(handles.ddic.readcutt);
handles.mat4,2 = num2str(handles.vSens(handles.ddic.cutt));
handles.mat4,3 = num2str(handles.vSpec(handles.ddic.cutt));
handles.mat4,4 = num2str(CP.ICVLdavid.EAIprod_App.Accuracy(handles.ddic.cutt));
handles.mat4,5 = num2str(CP.ICVLdavid.EAIprod_App.PPV(handles.ddic.cutt));
handles.mat4,6 = num2str(CP.ICVLdavid.EAIprod_App.NPV(handles.ddic.cutt));

    Data=handles.mat;
set(handles.Results,'data',Data);

    guidata(hObject,handles);
```

B

Previous publications