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Reassessing the Significance of Tumor Diameter and Surgical Approach in Predicting Recurrence of Early-Stage Cervical Cancer

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INDEX

INTRODUCTION

I. ANATOMY

The uterine cervix serves as a cylindrical structure, functioning as a conduit connecting the uterine cavity and the vagina. The cervical canal opens into the endometrial cavity at the internal orifice and into the vagina at the external os. In women of reproductive age, it comprises the inferior third of the uterus, while in prepubertal and postmenopausal women, the corpus and cervix exhibit similar sizes. However, the morphology and dimensions of the uterus may vary based on hormonal status, prior pregnancies, or the presence of uterine pathology (1).

The cervix is composed of connective tissue and smooth muscle, forming a continuous layer with the myometrium of the corpus. The ectocervix, which extends into the vagina, is lined with squamous epithelium; conversely, the internal layer of the endocervical canal is covered by glandular epithelium. The region where the epithelium transitions from squamous to glandular is referred to as the squamo-columnar junction. After menarche, hormonal changes expose the glandular epithelium of the endocervical canal to the acidic vaginal environment, leading to metaplastic transformation into squamous epithelium. This process establishes a new squamo-columnar junction. The area undergoing this transformation, situated between the old and the new squamo-columnar junction, is known as the transformation zone, and it represents the region most susceptible to dysplasia and cancerous lesions (1).

The cervix is anchored to the pelvic sidewall and the sacrum through the parametria, consisting of three bands of connective tissue: the posterior parametrium or uterosacral ligament, the cardinal ligament or lateral parametrium, and the cervico-vesical ligament or anterior parametrium. The cardinal ligaments extend from the cervix and upper vagina to the pelvic side wall, housing the uterine vessels along most of their course. The uterosacral ligaments run from the cervix, where the cardinal ligaments insert, to the sacrum. The ureter closely interacts with the uterosacral ligaments before crossing the uterine artery, while the hypogastric nerve courses 1-2 cm below the ureter and

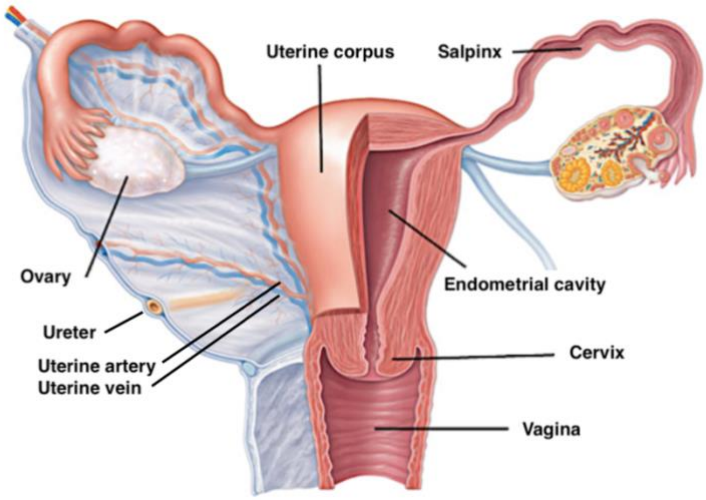
along the lateral aspect of the uterosacral ligament. The cervico-vesical ligament includes the ureteric tunnel that houses the ureter after passing under the uterine artery (1).

The uterine artery, an anterior branch of the internal iliac artery, supplies blood to the uterine corpus and cervix. It traverses from a lateral to medial direction through the lower part of the broad ligament, passing over the distal ureter within the lateral parametrium. At the isthmus level, it bifurcates into ascending and descending branches. The ascending branch extends laterally to the uterus, providing blood flow to the uterine corpus, and eventually forming an anastomosis with the ovarian artery. The descending branch supplies blood flow to the cervix and upper vagina and anastomoses with branches of the vaginal artery (1,2,3,4).

Similarly, uterine veins course through the broad ligaments and drain into the internal iliac veins, establishing anastomoses with the vaginal and ovarian veins (1).

Lymphatic drainage from the uterus and cervix primarily targets three major groups of lymph nodes: external iliac lymph nodes, internal iliac lymph nodes, and obturator lymph nodes (4).

Figure 1. Anatomy of the uterus and uterine adnexa.

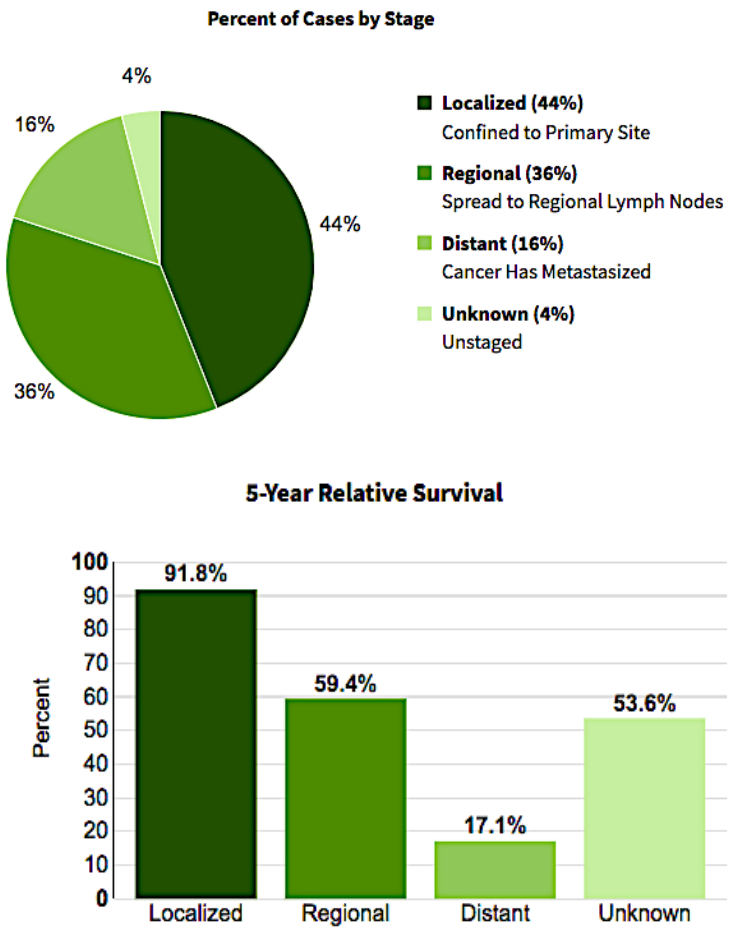


II. EPIDEMIOLOGY

Cervical cancer ranks as the fourth most prevalent malignancy among women worldwide, contributing to 6.6% of all female cancer cases and holding the fourth position in terms of mortality. In 2020, the global incidence recorded 604,127 new cases, resulting in 341,831 deaths due to the disease. Notably, Europe alone accounted for 58,169 new cases in 2020, leading to nearly 26,000 fatalities (5).When considering women of reproductive age, cervical cancer's incidence escalates to 12.6% of all cancer cases, positioning it as the second most common malignancy following breast cancer. Significantly, the likelihood of developing cervical cancer is higher in premenopausal women, gradually decreasing from 0.3% to 0.1% in women aged over 50 (6).

The implementation of extensive screening programs has contributed to a decline in cervical cancer rates in developed nations. However, substantial variations persist, influenced by factors such as race and ethnicity. Meanwhile, low-income countries continue to grapple with higher cervical cancer incidence (7) (8) (9). Regrettably, despite being one of the most preventable forms of cancer, cervical cancer persists as the second leading cause of cancer-related deaths among women aged 20 to 39 in developed countries (6). The estimated five-year survival rate in developed countries stands at 66.7%, exhibiting relative stability over the past decade. This survival rate is strongly contingent on the stage of the disease (10).

Figure 2. Distribution of cases by stage and 5-year survival of cervical cancer



III. NATURAL HISTORY OF THE DISEASE AND STAGING

The overwhelming majority of cervical cancers are linked to a persistent infection with high-risk human papillomaviruses (HPV). Human papillomaviruses are non-enveloped viruses that employ double-stranded DNA for replication within cutaneous and mucosal epithelia. They underlie a wide spectrum of diseases, ranging from benign lesions to premalignant and malignant conditions. There exist more than 200 subtypes of HPV, each with varying oncogenic potentials (11). Approximately 50% of cervical cancers are attributed to HPV-16, and 20% to HPV-18 (12). A persistent HPV infection within the basal layer at the squamo-columnar junction, facilitated by micro-trauma disrupting the stratified epithelium's continuity, initiates cellular changes leading to intraepithelial lesions (13) (14). These alterations progress from cellular atypia through intraepithelial lesions to invasive cancer. The duration of this process exceeds 10 years, allowing for the identification and treatment of precancerous lesions before they advance to invasive stages.

Squamous intraepithelial lesions are categorized as low grade (L-SIL) and high grade (H-SIL), with the grading dependent on the proportion of the epithelium containing mature and differentiated cells, which are often scarce or absent in more severe lesions. Precancerous lesions originating from columnar epithelium follow a similar pattern, advancing from adenocarcinoma in situ (AIS) to cervical adenocarcinoma.

Cytologic screening has proven effective in reducing cervical cancer incidence by detecting precancerous lesions that can be treated effectively before invasive tumors develop (15) (16). Currently, it is recommended to screen women over 30 years of age with an HPV DNA test, which detects the presence of high-risk HPV, to monitor the infection and its persistence before any damage to epithelial cells occurs (17). Cigarette smoking, whether active or passive, increases the risk of cervical cancer, although the precise mechanism underlying this correlation remains unclear. Factors such as lower socioeconomic status, advanced age, and obesity are independently

associated with restricted access to cytologic screening, thus correlating with higher rates of cervical cancer.

In cases of invasive lesions, patients may present with abnormal vaginal discharge, irregular uterine bleeding, or postcoital bleeding. Asymptomatic lesions may also be incidentally detected through pelvic examination or imaging. Locally advanced disease may manifest with pelvic pain or symptoms related to the compression of veins, lymphatics, nerves, or ureters, such as lower limb edema, lower back pain, or hydronephrosis. Invasion of the bladder or rectum may lead to blood discharge from these organs and the formation of vesicovaginal or rectovaginal fistulas. In some instances, patients with locally advanced malignancies may experience profuse cervical bleeding.

During pelvic examination, irregularities in cervical morphology and consistency may be observed, along with necrotic or friable exophytic lesions. A rectovaginal examination should be performed to assess the extent of involvement in the vaginal mucosa, parametria, and pelvic sidewalls. Any abnormal findings should be followed by a biopsy to obtain a histologic diagnosis.

Cervical cancer exhibits aggressive local spread, commonly extending to the parametria, vagina, and adjacent organs, including the bladder and rectum. It also involves lymphatic spread, initially affecting regional lymph nodes such as the obturator, external iliac, and internal iliac lymph nodes before progressing to the common iliac and para-aortic lymph nodes. Hematogenous spread is a late-stage occurrence, typically affecting the lungs, liver, and bones.

The treatment strategy is tailored based on the disease's stage. According to established guidelines, the imaging evaluation should encompass pelvic MRI and a total body PET scan. MRI provides critical information on tumor size, depth of stromal invasion, and involvement of adjacent tissues, while a PET scan assesses nodal status and potential distant spread (18) (19) (20). Until 2018, the International Federation of Gynecology and Obstetrics (FIGO) staging system primarily relied on clinical examination, with nodal status not influencing the disease stage.In 2018, a new FIGO

staging system was adopted (as depicted in Table 1). This revised classification incorporates multiple clinical, imaging, and pathological findings to accurately determine the stage (21).

Table 1. FIGO staging of cancer of the cervix uteri (2018)

Stage			Description
I			The carcinoma is strictly confined to the cervix
	IA		Invasive carcinoma that can only be diagnosed by microscopy, with maximum depth of invasion <5mm
		IA1	Measured stromal invasion <3mm in depth
		IA2	Measured stromal invasion ≥3mm and <5mm in depth
	IB		Invasive carcinoma with measured deepest invasion ≥5mm, lesion limited to the cervix uteri
		IB1	Invasive carcinoma ≥4mm depth of stromal invasion, <2cm in greatest dimension
		IB2	Invasive carcinoma ≥2cm and <4cm in greatest dimension
		IB3	Invasive carcinoma ≥4cm in greatest dimension
II			The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
	IIA		Involvement limited to the upper two-thirds of the vagina without parametrial involvement
		IIA1	Invasive carcinoma <4cm in greatest dimension
		IIA2	Invasive carcinoma ≥4cm in greatest dimension
	IIB		With parametrial involvement but not up to the pelvic wall
III			The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes
	IIIA		The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
	IIIB		Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to other causes)
	IIIC		Involvement of the pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)
		IIIC1	Pelvic lymph node metastasis only
		IIIC2	Para-aortic lymph node metastasis
IV			The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum
	IVA		Spread to adjacent organs
	IVB		Spread to distant organs

IV. HISTOLOGY

Cancer of the cervix may originate both from the squamous epithelium of the ecto-cervix and the glandular epithelium of the endocervical canal, however, most of the malignancies arise within the transformation zone.

Table 2. 2020 WHO classification of cervical tumors

Squamous cell tumors
Squamous intraepithelial lesions
Squamous cell carcinoma, HPV-associated
Squamous cell carcinoma, HPV-independent
Squamous cell carcinoma NOS
Adenocarcinomas
Adenocarcinoma in situ, HPV-associated
Adenocarcinoma, HPV-associated
Adenocarcinoma in situ, HPV-independent
Adenocarcinoma, HPV-independent, gastric type
Adenocarcinoma, HPV-independent, clear cell type
Adenocarcinoma, HPV-independent, mesonephric type
Other adenocarcinomas
Other epithelial tumors
Carcinosarcoma
Adenosquamous and mucoepidermoid carcinomas
Adenoid basal carcinoma
Unclassifiable carcinoma
Mixed epithelial and mesenchymal tumors
Adenomyoma
Adenosarcoma
Germ cell tumors

Squamous cell carcinomas account for over 70% of cervical cancers, with adenocarcinomas representing approximately one-quarter of cervical malignancies. Squamous cell carcinomas typically manifest as exophytic growths but, on occasion, may exhibit an endophytic pattern within the endocervical canal (22). Various subtypes of these tumors have been described; however, the current classification primarily revolves around their association with HPV infection. To distinguish between these forms, the 2020 World Health Organization (WHO) recommends utilizing immunohistochemistry, as hematoxylin-eosin staining alone does not enable differentiation between the two categories. Based on immunohistochemistry results obtained using markers such as p16,

p53, and HPV-PCR, squamous cell carcinomas are classified as either HPV-associated or HPV-independent (23). In cases where immunohistochemistry is not feasible, a classification as "squamous cell carcinoma NOS" (Not Otherwise Specified) is acceptable. For adenocarcinomas, the use of immunohistochemistry with p16 is not obligatory, as it may yield positive results in both HPV-associated and HPV-independent tumors, owing to its role as a tumor suppressor gene. HPV-associated adenocarcinomas are categorized according to the Silva pattern (24) (25) (26), a classification grounded in architectural features. This classification is linked to prognosis, the risk of lymph node metastasis, and recurrence, as detailed in Table 3. The Silva classification segregates invasive adenocarcinomas into three patterns (A, B, and C) based on the presence and degree of destructive stromal invasion, the presence of lympho-vascular invasion, and the grade of cytologic atypia.

Table 3. The Silva pattern classification

Pattern	Architectural characteristics	Frequency	Stage I	Recurrence
A	No destructive stromal invasion Well-demarcated glands with rounded contour No single cells or cell detachment Complex intraglandular growth <5 mm No solid growth or high-grade cytology No LVSI	20%	99%	0%
B	Localized destructive stromal invasion arising from well-demarcated glands Individual glands or small clusters of tumor cells, separated from rounded glands, usually in an inflamed or desmoplastic stroma Foci of localized destructive <5 mm No solid growth LVSI present or absent	20%	91%	3%
C	Diffuse destructive invasion Infiltrative glands, variable in shape and size Confluent growth Irregular glands or papillary structure with little intervening stroma or mucin lakes with tumor cells ≥5 mm Solid growth Poorly differentiated component (high grade) Tumor cells or individual glands present in a desmoplastic stroma at the base of the tumor Band-like lymphocytic infiltrate LVSI present or absent	60%	65%	19%

V. PRIMARY TREATMENT

The selection of an appropriate treatment for cervical cancer hinges on the disease's stage. Early-stage cancers, up to IB2 FIGO 2018, are typically managed with surgical interventions. In contrast, locally advanced tumors are best treated with a combination of radiotherapy and concurrent chemotherapy. Advanced stages featuring distant metastasis may necessitate systemic chemotherapy before undergoing chemoradiation therapy.

Stage IA1-2 cervical cancers are characterized by a minimal risk of tumor spread and an exceedingly low rate of nodal metastasis, making them suitable for conservative treatment. According to NCCN (18) and ESGO-ESTRO-ESP (20) guidelines, patients with stage IA1 cervical cancer lacking lympho-vascular space invasion (LVSI) can be safely treated with conization. Meanwhile, sentinel lymph node (SNL) mapping or pelvic lymphadenectomy is recommended for patients with LVSI and stage IA2. Conization should be adapted to ensure complete lesion removal and negative margins, preferably performed via a cold knife approach. The loop electrosurgical excision procedure (LEEP) may be acceptable as long as it achieves sufficient margins and minimizes heat artifacts. When fertility preservation is not a concern, a simple hysterectomy is the preferred treatment. In adenocarcinomas, according to the latest ESGO guidelines, hysterectomy should be offered to patients who have completed childbearing, even after fertility preservation treatments.

For stage IB1-IB2 cervical cancer, radical hysterectomy with bilateral pelvic lymphadenectomy is the primary treatment option when fertility preservation is not a priority. In select cases, conservative surgery with trachelectomy or conization may be considered, necessitating different approaches to ensure complete tumor removal. In stage IB2 cervical cancer, patients should receive comprehensive counseling regarding the expected benefits and potential risks of the procedure, particularly the potential need for adjuvant therapy, which may impact future fertility.

In specific instances, IB3 or IIA1 tumors may be surgically treated if complete resection is feasible. The preferred treatment strategy should aim to avoid the combination of radical surgery and radiotherapy to reduce morbidity.

For locally advanced stages, concurrent radiochemotherapy is the standard of care (27). This combined approach surpasses radiation therapy alone in terms of local control, freedom from metastasis, disease-free survival, and overall survival. External beam radiation therapy (EBRT) is planned based on imaging (using MRI or PET) to target tumor-involved areas. Concurrent platinum-based chemotherapy, typically cisplatin monotherapy at 40 mg/m2 on a weekly schedule, is administered during EBRT. Brachytherapy, whether interstitial or intracavitary, is an essential component of definitive radiation therapy, usually following EBRT. It delivers high doses to the remaining tumor while sparing the bladder, rectum, and sigmoid.

Patients presenting with metastatic disease are typically treated with platinum-based chemotherapy. Individualized EBRT may be employed to manage pelvic disease and related symptoms (20) (18).

1. Surgical treatment: radical hysterectomy

Radical hysterectomy (RH) is a surgical procedure that involves the removal of the uterus, cervix, upper part of the vagina, and adjacent parametrial and paracervical tissues. The choice of additional procedures, such as bilateral salpingectomy or bilateral salpingo-oophorectomy, depends on the patient's age and tumor characteristics. Ovarian preservation is typically considered for premenopausal women with squamous carcinoma or HPV-related adenocarcinoma.

Historically, various degrees of radicality in hysterectomy have been described since the first reports by surgeons like Wertheim (28), Okabayashi (29), and Meigs (30). To standardize the classification of parametrial resection and nerve preservation in radical hysterectomy, the Querleu-Morrow system was introduced in 2008 (31) and revised in 2017 (32) and is currently the accepted standard (see Table 4).

Type A radical hysterectomy focuses on complete removal of the cervix down to the vaginal fornix, leaving a paracervical margin. It differs from a simple "extrafascial hysterectomy" as it involves direct visualization of the ureter's position, with dissection of the paracervix occurring between the ureter and cervix. This type involves minimal vaginal resection and does not require paracolpium resection. The rectovaginal and vesicovaginal ligaments are partially resected but not at the bladder or rectum.

Type B radical hysterectomy includes the unroofing of the ureter and its lateral mobilization, allowing for resection of the paracervix at the level of the ureteral tunnel. It also involves partial resection of the uterosacral peritoneal fold of the rectouterine ligament and the vesico-uterine ligament. Approximately 10 mm of the vagina, starting from the caudal edge of the cervix or tumor, is resected. In B2 radical hysterectomy, paracervical lymphadenectomy is added.

Type C radical hysterectomy extends to the lateral resection along the medial aspect of the iliac vessels. This type involves the development of the medial and lateral pararectal spaces and the

lateral paravescical spaces, along with resection of the caudal part of the paracervix. Bladder and hypogastric nerves are identified and preserved in type C1 but sacrificed in type C2. Type C hysterectomy also entails removal of the upper third of the vagina and the paracolpium.

Type D radical hysterectomy is a less common approach, typically performed in combination with other radical procedures as part of pelvic exenteration for recurrent tumors.

Table 4. Types of radical hysterectomy (adapted from Querleu et al, 2017)

Type of RH		**Paracervix or lateral parametrium**	**Ventral parametrium**	**Dorsal parametrium**
A		Halfway between the cervix and the ureter (medial to the ureter; ureter identified but not mobilized)	Minimal excision	Minimal excision
B	B1	At the ureter (at the level of the ureteral bed; ureter mobilized from the cervix and lateral parametrium)	Partial excision of the vescico-uterine ligament	Partial resection of the rectouterine-rectovaginal ligament and uterosacral peritoneal fold
	B2	Identical to B1 plus paracervical lymphadenectomy without resection of vascular/nerve structure	Identical to B1	Identical to B1
C	C1	At the iliac vessels transversally, caudal part is preserved	Excision of the vescico-uterine ligament at the bladder; proximal part of the vescico-vaginal ligament (bladder nerve dissected and spared)	At the rectum (hypogastric nerve dissected and spared)
	C2	At the level of the medial aspect of iliac vessel (caudal part included)	At the bladder (bladder nerves sacrificed	At the sacrum (hypogastric nerve sacrificed)
D		At the pelvic wall, including resection of the internal iliac vessels and components of pelvic sidewall	At the bladder	At the sacrum

The choice of the specific type of radical hysterectomy and the extent of lateral parametrial resection is determined based on the identification of preoperative prognostic risk factors. These risk factors, including tumor size, depth of stromal invasion, and lymphovascular space invasion

(LVSI), are used to categorize patients into high, intermediate, or low-risk groups for treatment failure.

Patients with tumors smaller than 2 cm, with negative LVSI, and stromal invasion limited to the inner third, are classified as low-risk. For these patients, the recommended procedure is a B1 radical hysterectomy. Patients at intermediate risk, such as those with tumors larger than 2 cm with negative LVSI or tumors smaller than 2 cm with positive LVSI, are typically candidates for a B2 radical hysterectomy, although selected cases may be considered for a C1 procedure. High-risk patients, characterized by tumors larger than 2 cm with positive LVSI, are advised to undergo a type C1 radical hysterectomy.

2. Nodal staging

Nodal staging considerations differ based on cancer stage and LVSI status. Patients with IA1 LVSI-negative cervical cancer typically do not require nodal staging. However, nodal staging may be considered for IA1 LVSI-positive and IA2 LVSI-negative patients. In these cases, sentinel lymph node biopsy, without the need for systematic pelvic lymphadenectomy, may be considered as a suitable approach. If the sentinel lymph node is not identified, a side-specific lymphadenectomy should be performed as recommended by the Memorial Sloan-Kettering Cancer Center. Additionally, any suspicious lymph nodes should be removed, irrespective of whether they were identified through mapping (33).

For all other patients undergoing surgical treatment, the standard procedure for lymph node staging is systematic bilateral pelvic lymphadenectomy. The nodal status can be assessed intraoperatively through the frozen section analysis of the sentinel lymph node or any suspicious nodes. This comprehensive procedure involves the removal of all fatty lymphatic tissue in various regions, including the common iliac, external iliac, internal iliac, obturator, and presacral regions (34).

In the common iliac region, the boundaries extend from the aortic bifurcation dorsally to the bifurcation of the common iliac vessels ventrally. The lateral border is defined by the psoas muscle, while the medial border is the mesoureter on the left side and the medial aspect of the common iliac vessels on the right side.

External iliac lymph nodes are removed by dissecting the fatty lymphatic tissue cranially, laterally, and medially from the external iliac vessels and between them. The ventral border extends to the origin of the deep circumflex iliac vein, and the dorsal limit is set at the common iliac artery bifurcation level. Internal iliac lymph nodes are resected medially to the internal iliac vein, with boundaries defined by the course of the internal iliac vessels cranially and laterally and the sacral bone caudally.

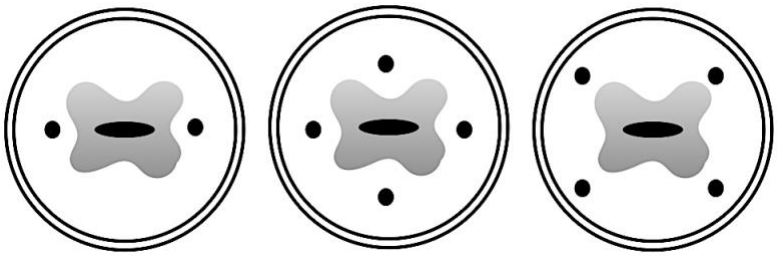
The obturator fossa boundaries are determined cranially by the caudal wall of the external iliac vein and caudally by the obturator vessels. The ventral border comprises the pubic bone, levator ani, and obturator muscles, while the dorsal limit extends to the common iliac vessels' bifurcation level, medial to the paravescical space. The presacral region's boundaries are set by the common iliac vessels' course cranially and laterally, the sacral bone caudally, and the sacral bone dorsally. Systematic pelvic lymphadenectomy is a complex surgical procedure associated with perioperative complications such as vascular or neurologic injuries, as well as delayed morbidities like lymphedema and lymphocysts. The procedure also results in longer operative times. Postoperative complications, including postoperative ileus, venous thromboembolism, and extended hospital stays, have been reported. Importantly, these complications can have long-term consequences, negatively impacting patients' quality of life (35). Approximately 20% of patients undergoing pelvic lymphadenectomy develop lower limb lymphedema, which is a permanent condition associated with psychological distress, including anxiety, depression, and adjustment disorder (36).

2.1. Sentinel lymph node

Sentinel lymph node (SNL) mapping is recommended by international guidelines as a part of surgical management in cervical cancer. The procedure has been used in tumors up to 4 cm, however the best rate detection has been shown in tumors smaller than 2 cm. (37) (38) (39) The technique includes injection into the cervix with either blue dye combined with radiocolloid technetium-99 or indocyanine green. The sites of injection of the tracer are shown in Figure 3.

Ultrastaging in sentinel lymph nodes is indicated because it allows a higher detection of micrometastasis, which will influence the pathologic stage and postoperative management. (18) (20)

Figure 3. Sites of cervical injection for SNL detection



Aiming to explore the role of SNL alone for nodal staging in early-stage cervical cancer, the SENTICOL trial analyzed its diagnostic accuracy and reported a 92% sensitivity and 98,2% negative predictive value. Therefore, the authors concluded that negative SNL can accurately predict the absence of nodal metastasis, but only if SNLs are detected bilaterally. (40)

As shown by the SENTIX trial, a multicenter prospective observational trial, great accuracy in detecting bilateral SNL can be obtained in the hands of experienced surgeons. The authors reported one of the highest detection rates with a 91% of bilateral detection and a median of 3 SNL removed per patient. Various techniques were used to detect SNL and indocyanine green was associated with a higher rate of successful detection. No SNL was found outside of the standard anatomical regions

included in the pelvic lymphadenectomy and the majority were detected either in the external iliac or obturator region. (41)

However, at present, the role of SNL alone is being further investigated and systematic pelvic lymphadenectomy remains the standard of care.

3. Surgical approaches to radical hysterectomy

Since their introduction in the clinical practice, minimally invasive techniques were adopted both in benign and oncologic surgery to reduce perioperative morbidity of laparotomic procedures. Mirroring the shift from open to minimally invasive surgery (MIS) in other malignancies, minimal access techniques gained widespread acceptance as an approach to radical hysterectomy for cervical cancer. Thus, the percentage of radical hysterectomy performed with MIS in cervical cancer rose starting from 2006 to reach approximately 60% in 2018.

This change in the surgical approach was validated by a number of retrospective studies and even two meta-analyses, that showed how minimally invasive approach was associated with less intraoperative blood loss, a shorter hospital stay and a lower risk of postoperative complications, while no significant differences between the two approaches were noted in terms of recurrence rates and survival rates. (42) (43) (44) (45) (46)

However, in November 2018, the publication of two studies on the New England Journal of Medicine deeply impacted the clinical practice in cervical cancer and lead to a reversal to open surgical approach.

In the first study, Melamed et al analyzed data from the USA National Cancer Database and reported a significant decrease in overall survival in women undergoing MIS radical hysterectomy in comparison to open surgery. Moreover, they showed that the decrease in survival in women affected by cervical cancer coincided with the wider adoption of MIS after 2006. (47)

The second study was the first randomized controlled trial conducted on the surgical approach in early-stage cervical cancer: the LACC trial (Laparoscopic Approach to Cervical Cancer). (48)

3.1 LACC trial

This phase III randomized trial, conducted by Ramirez et al, was undertaken to examine disease-free survival in patients undergoing minimally invasive surgery (MIS) as compared to those treated with open surgery. The trial was structured as a non-inferiority study of MIS versus open surgery, with the primary outcome being disease-free survival at 4.5 years. Secondary objectives included evaluating the rates of disease recurrences and overall survival (49).

The study encompassed patients with stage IA1 with LVSI, IA2, or IB1 (FIGO 2009) cervical cancer, while histologic subtypes other than adenocarcinoma, squamous cell carcinoma, or adenosquamous carcinoma were excluded. Patients from around the world were randomly assigned to either minimally invasive or open surgery (49). Unexpectedly, in 2017, patient enrollment was halted prematurely due to an alert from the data and safety monitoring committee regarding an imbalance in deaths between the two groups. Subsequent follow-up confirmed these findings, leading to the permanent closure of the trial to new enrollment, with 631 eligible patients enrolled out of the initially planned 740 (49).

Survival at 4.5 years exhibited significant differences between the two groups, with rates ranging from 86% in the MIS group to 96.5% in the open-surgery group. Moreover, MIS was associated with lower overall survival rates, a higher mortality rate, and an increased rate of locoregional recurrences. Examining the results in detail revealed a hazard ratio for disease recurrence or death from cervical cancer of 3.74 in the MIS group compared to open surgery and loco-regional recurrence were more than four times as frequent in patients treated with MIS. Considering overall survival, the risk of death by any cause was six times higher in the MIS group compared to open surgery (49). These findings were subsequently corroborated through further observation with

extended follow-up. In response to this evidence, international guidelines were revised to recommend the open approach for cervical cancer surgery, leading surgeons worldwide to revert to open surgery for cervical cancer (49).

Criticism of this trial primarily centered around the low recurrence rates observed in the open-surgery group, the surgical proficiency required for performing adequate radical hysterectomies, and potential confounding factors in the surgical techniques, such as the use of uterine manipulators or colpo-protective maneuvers. These concerns were rooted in the study's design; however, subsequent systematic reviews affirmed the LACC trial's findings. In 2020, three separate meta-analyses provided further evidence, indicating significantly lower rates of disease-free and overall survival in MIS compared to open surgery in cervical cancer (50) (51).

The LACC trial also yielded data on adverse events and quality of life post-surgery in cervical cancer. Despite previous studies suggesting that minimally invasive surgery was associated with superior surgical outcomes, the LACC trial showed that intraoperative and postoperative complications did not differ significantly between the MIS and open-surgery groups (52). Quality of life assessments conducted at 6 weeks and 3 months after surgery did not reveal any significant differences between MIS and open surgery for all patients enrolled in the LACC trial (53).

To assess the clinical impact of the LACC trial, Bogani et al conducted a multicenter retrospective study, providing data on complications within 90 days before and after the trial (54). Their report indicated a decrease in patients treated with MIS from 64.9% to 30.4%. All participating centers reported adopting protective measures to reduce the risk of disease dissemination during minimally invasive radical surgery, such as preoperative conization, avoidance of uterine manipulator use, and vaginal cuff closure before colpotomy. The study confirmed data from secondary outcomes of the LACC trial, as it showed no difference in intraoperative or 90-day postoperative complications, even after stratification by the stage of the disease. Furthermore, they observed similar operative

times for MIS and open surgery, with only blood loss and postoperative recovery time demonstrating significant differences, albeit relatively modest ones (54).

3.2 SUCCOR trial

The publication of the LACC trial results in 2018 was a groundbreaking moment in the field of cervical cancer treatment, leaving many surgeons taken aback by the unexpected findings. To gauge the impact of the LACC trial on cervical cancer treatment practices, the European Society of Gynecological Oncology (ESGO) conducted a survey in 2019 among its members, aiming to understand their perspectives (55). The survey revealed that 83% of participants were not anticipating these results, and a significant majority (56%) made a swift switch in their surgical approach from minimally invasive to open surgery within the first four months after the LACC trial was published. However, in Europe, updated information on the outcomes of radical hysterectomy based on the surgical approach was lacking. In this context, Chiva and colleagues initiated the SUCCOR trial (56), a retrospective international cohort study designed to evaluate disease-free survival (DFS) in patients with stage IB1 (FIGO 2009) cervical cancer, comparing minimally invasive surgical approaches to open surgery. As secondary objectives, the study sought to assess the risk of relapse between these two approaches and explore the potential impact of protective maneuvers, such as avoiding the use of a uterine manipulator and employing protective vaginal closure before colpotomy, in minimally invasive surgery. Additionally, the analysis examined subgroups of patients based on tumor size, postulating that differences in tumor size could influence survival disparities observed between MIS and open surgery.

Data encompassing patients who underwent radical hysterectomy for cervical cancer between January 1st, 2013, and December 31st, 2014, were gathered from 126 institutions across 29 European countries. The median follow-up period was 59 months. The inclusion criteria were patients over 18 years of age with a diagnosis of squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix. All patients underwent imaging staging with pelvic MRI

to confirm a tumor diameter less than or equal to 4 cm and the absence of parametrial invasion. Preoperative imaging, which included MRI, CT scans, or PET-CT, was mandatory to rule out extra-cervical metastatic disease. Exclusion criteria encompassed a prior history of cancer, previous chemotherapy or radiation therapy, and the presence of suspicious nodes or metastatic disease on preoperative imaging. The operative report needed to detail either a type B or a type C radical hysterectomy with a bilateral pelvic lymphadenectomy, involving at least 10 pelvic nodes. Patients who underwent sentinel lymph node biopsy were also included, while exclusion criteria included conversion from minimally invasive surgery to open surgery and conization prior to radical hysterectomy. The final survival analysis, involving 693 patients, reinforced the findings of the LACC trial and demonstrated a less favorable prognosis in the minimally invasive surgery group. Disease-free survival (DFS) was 79% in the MIS group compared to 89% in the open surgery group, and MIS was linked to a lower rate of overall survival (OS). The risk of recurrence in the MIS group was twice that of the open surgery group, and the risk of death was 2.42 times higher. In a subanalysis considering subgroups of patients with tumors larger or smaller than 2 cm, all results were consistent for tumors larger than 2 cm, while in patients with smaller tumors, the differences in DFS, OS, and recurrence were not statistically significant.

The use of a uterine manipulator had an adverse effect on survival (both DFS and OS) and increased the rate of relapses by 2.76 times. These discrepancies were confirmed in patients with tumors larger than 2 cm but were not evident in patients with tumors ≤2 cm. In contrast, patients who underwent minimally invasive surgery with protective vaginal closure, a procedure aimed at preventing tumor spillage during colpotomy, exhibited a recurrence rate similar to the open surgery group. However, these differences were observed in the group of patients with tumors ≥2 cm but were not observed in patients with smaller tumors.

VI. ADJUVANT THERAPY

Adjuvant treatment is indicated after radical hysterectomy according to stage of the disease and surgical findings.

In patients with the following risk factors concomitant chemoradiation therapy is indicated as adjuvant treatment:

- Metastatic lymph node involvement, either micrometastasis or macrometastasis
- Positive surgical margins (vaginal or parametrial margins)
- Parametrial involvement

These so-called Peters criteria were identified by a study conducted by Peters et al in 2000 (57) that demonstrated that, in this setting of patients, the addition of cisplatinum-based chemotherapy to external beam pelvic radiation therapy confers benefits in terms of both disease free survival and overall survival.

In patients with negative lymph-nodes, negative surgical margins and without parametrial involvement radiotherapy is indicated according to risk factors for recurrence.

In 1999, Sedlis et al (58) conducted a randomized trial including patients with IB cervical cancer with negative lymph nodes, presenting one or more of the potential risk factors for recurrence identified from the literature: larger tumor diameter, deep stromal invasion and lympho-vascular space invasion. They found that, adjusting for a combination of the aforementioned risk factors, the risk of recurrence was significantly reduced by radiation therapy and therefore identified the groups of patients who may benefit the most from this treatment.

The Sedlis criteria are now commonly adopted in the clinical practice and are included in international guidelines as indications to postoperative radiotherapy (Table 5).

Table 5. Sedlis criteria

Lympho-vascular invasion	Stromal invasion	Tumor size (cm)
+	Deep third	Any
+	Middle third	≥2
+	Superficial third	≥5
-	Deep or middle third	≥4

Potential risk factors for recurrence may not only be limited to these criteria, and additional risk factor may be taken into account when counselling a patient for adjuvant treatment, such as histology (e.g. adenocarcinoma) or close or positive surgical margins.

When indicated, EBRT (external beam radiation therapy) is planned according to imaging (either with MRI or PET) to be directed to the sites of tumor involvement. Additional brachytherapy may be considered in case of a high risk of local recurrence.

In the absence of said pathologic risk factors observation is appropriate.

AIM OF THE STUDY

Since the GOG randomized trial conducted in 1999, the Sedlis criteria have become widely adopted for deciding on adjuvant treatment in patients with negative lymph nodes, clear margins, and intact parametria. However, existing treatment guidelines often allow clinicians to assess additional risk factors based on histology or patient characteristics without clearly specifying these parameters.

Furthermore, inconsistent rates of adjuvant treatment following radical hysterectomy have been reported in numerous retrospective studies, ranging from 18% to 33% (59) (60) (47) (61) (62) (63). Even within the population of the LACC trial, which is the most relevant recent randomized controlled trial in cervical cancer, 28% of patients received adjuvant therapy, with 18% receiving chemoradiation (48). It's important to note that these trials included patients with FIGO stage IA cervical cancer, which could account for the lower rate of adjuvant treatment.

An analysis of data from the SUCCOR study, which specifically focused on patients with IB1 (FIGO 2009) cervical cancer treated in Europe from 2013 to 2014, revealed higher rates of adjuvant treatment than previously described in the literature. In this cohort, 44.1% of patients received adjuvant therapy. Among these, 71.8% did so due to positive pelvic lymph nodes, parametrial extension, positive surgical margins, or because they were classified as intermediate risk according to Sedlis criteria. The remaining 28.2% received adjuvant therapy without meeting any of the conventional criteria for such treatment; their indications for adjuvant therapy were linked to factors such as depth of invasion, lymphovascular space invasion, histological grade, and tumor size. Importantly, the specific indications for adjuvant treatment were at the discretion of the physicians in each institution, potentially varying between centers.

Additionally, in the analysis of patients who experienced recurrences, exactly 50% of them had received adjuvant therapy after surgery. These findings raise concerns about the lack of consensus

among gynecologic oncologists worldwide when it comes to the administration of adjuvant radiation therapy following radical hysterectomy for stage IB1 (FIGO 2009) node-negative cervical cancer. Furthermore, it underscores the need for further investigation to determine whether there may be an issue of overtreatment with radiation therapy that doesn't necessarily translate to improved survival.

Given this context, the primary objective of our study was to assess the factors associated with the administration of adjuvant therapy after radical hysterectomy for stage IB1 (FIGO 2009) node-negative cervical cancer. As a secondary objective, we aimed to investigate the factors linked to recurrence in the same patient group, as well as in the subgroup of patients who did not undergo adjuvant radiation therapy, in order to assess the impact of adjuvant radiation therapy on disease-free survival for patients with stage IB1 (FIGO 2009) node-negative cervical cancer.

METHODS

In this study, we conducted an analysis of patient data sourced from the SUCCOR study. The original SUCCOR database encompassed information from patients who had undergone radical hysterectomy for stage IB1 (FIGO 2009) cervical cancer in European healthcare institutions within a specified time frame, namely, from January 1st, 2013 to December 31st, 2014, with a follow-up period of 5 years. A total of 126 healthcare institutions across 29 European countries participated in this collaborative effort.

The inclusion criteria for the SUCCOR trial were as follows: eligible patients were aged 18 years or older and diagnosed with squamous cell carcinoma, adenocarcinoma, or adeno-squamous carcinoma of the cervix. All patients underwent rigorous imaging staging involving pelvic MRI to confirm a tumor diameter of less than or equal to 4 cm, as well as the absence of parametrial invasion. Furthermore, diagnostic modalities such as MRI, CT scan, or PET-CT were performed to rule out the presence of extra-cervical metastatic disease. Patients with a prior history of cancer, those who had received previous chemotherapy or radiation therapy, and individuals with suspicious nodes or documented metastatic disease on preoperative imaging were explicitly excluded.

Within the original database, each patient's demographic characteristics and comprehensive information regarding preoperative evaluation, intraoperative particulars, and the pathology report were meticulously documented. For the purposes of our current analysis, we specifically focused on patients who did not exhibit nodal involvement according to the definitive pathology report, resulting in a total of 990 patients included in our initial dataset. Patients presenting with parametrial or vaginal involvement were subsequently excluded from our study. If any essential data pertaining to variables such as lympho-vascular invasion, depth of invasion, adjuvant therapy, or relapse status were absent in the patient records, those individuals were also omitted from the

analysis. By applying these stringent criteria, we ultimately derived a definitive study population comprising 572 patients. A visual representation of the selection process is provided in Figure 4.

Within this well-defined database, we gathered demographic attributes of the patients, including age, Body Mass Index (BMI), which is calculated as the ratio of an individual's weight in kilograms to the square of their height in meters, and their performance status. The assessment of performance status was conducted in accordance with the ECOG (Eastern Cooperative Oncology Group) Performance Status Scale.

Table 6. ECOG Performance Status **(64)**

0	Fully active, able to carry on all pre-disease performance without restrictions
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair for more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

The data pertaining to the surgical procedure encompassed a comprehensive set of variables, which included whether the patient had previously undergone conization, the chosen surgical approach (open or minimally invasive surgery, either laparoscopic or robotic), the implementation of protective maneuvers, the type of hysterectomy performed, denoted as either type B or type C based on the Querleu-Morrow classification, the number of pelvic lymph nodes removed during lymphadenectomy, and whether a sentinel lymph node biopsy was conducted. Detailed records of intraoperative and postoperative complications were also documented.

As for the pathology report, our analysis encompassed the histologic type and tumor grading. Tumor diameter was reported both as an absolute numeric value and categorized as smaller or larger than 2 cm, mirroring the approach outlined in the new FIGO 2018 classification for IB1 and

IB2 stage. Variables such as tumor diameter, lympho-vascular space invasion, and depth of invasion were examined individually and in combination, consistent with the Sedlis criteria.

Additionally, our study recorded instances of adjuvant treatment, disease relapses, and deaths related to the disease within the 5-year follow-up period.

In our data analysis, continuous variables were expressed as median values with corresponding ranges, while categorical variables were presented as absolute counts and percentages.

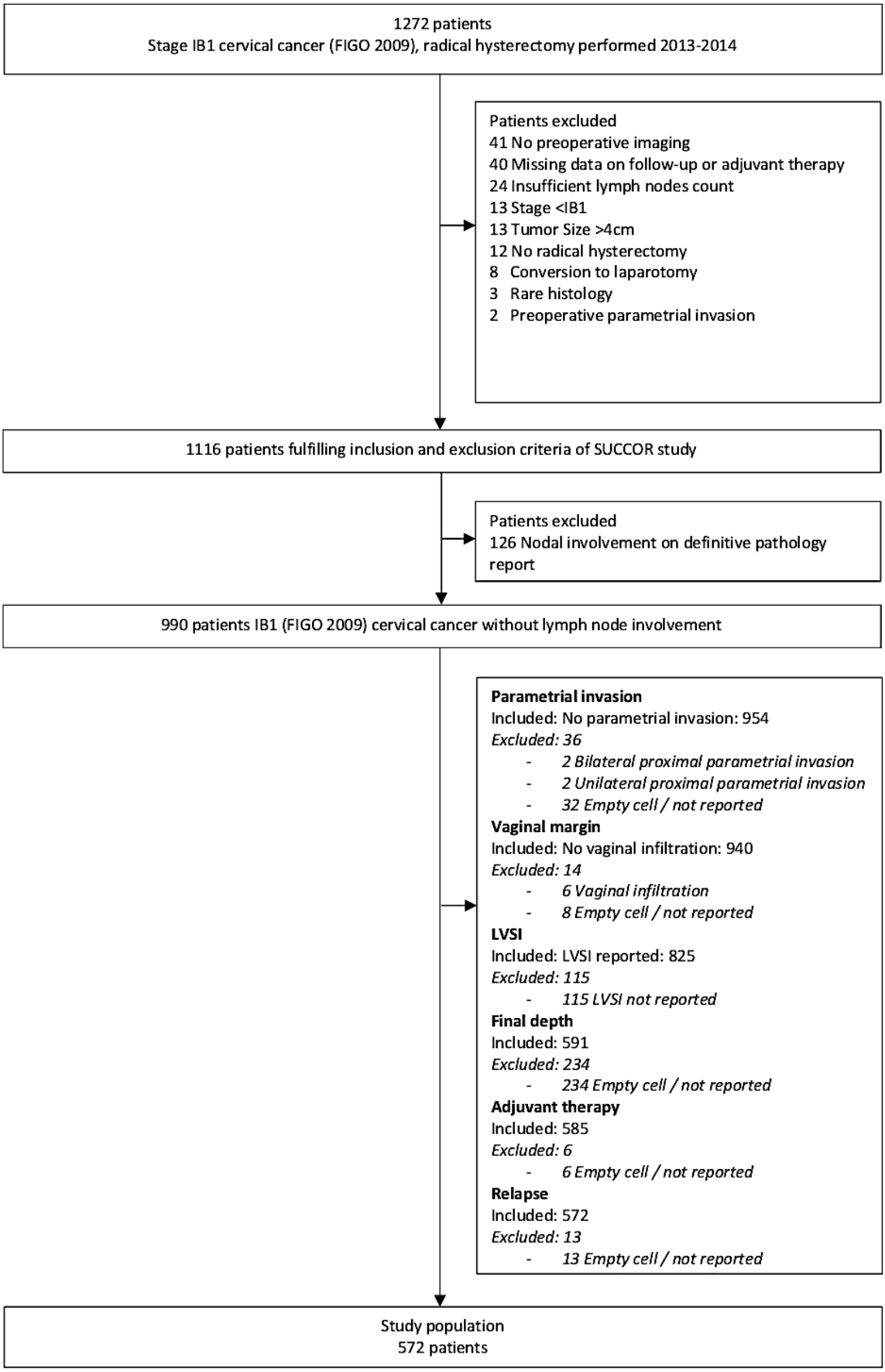
To describe the study populations, we employed basic descriptive statistics. When comparing two groups, differences in categorical variables were assessed using the Fisher exact test, while for comparisons involving three or more groups, the Chi-square test was applied. For continuous variables, the t-test and Mann-Whitney tests were used as appropriate. A significance level of $P < 0.05$ was employed to denote statistical significance.

In order to account for potential confounding factors, a multivariable analysis was carried out, incorporating variables that exhibited significant differences in the univariate analysis, along with clinically relevant parameters. The results of the models were expressed as odds ratios (OR) and 95% confidence intervals (95% CI).

Furthermore, multivariable analysis with Cox proportional hazard ratios (HR) was conducted to explore the factors associated with adjuvant radiotherapy and factors linked to disease recurrence. We reported disease-free survival (DFS) using Kaplan-Meier survival analysis.

The statistical analysis was performed using JMP software (JMP Pro, SAS Analytics).

Figure 4. Flowchart of the study population



RESULTS

I. BASELINE CHARACTERISTICS OF THE STUDY POPULATION

Baseline characteristics of the 572 patients included in our study were analyzed (details shown in Table 6).

The median age of the patients was 46 years and 60.5% of the population was younger than 50 years. This data reflects the incidence of cervical cancer in the general population in Europe, that rises sharply from around age 15-19 and peaks in the 30-34 age group, then drops until age 50-54. (65)

The median BMI in our population was 25 and 43.4% of the women involved were overweight or obese. This data is also consistent with the characteristics of the general population in Europe. Indeed, in the period considered, the European Health Interview Survey reported that 35.7% of the adults in Europe were pre-obese (BMI 25-30) and 15.9% were obese (BMI >30). (66)

Since the database refers to a period prior to the publication of the LACC trial, it is not surprising to note that 43.5% of women underwent minimally invasive surgery. More than two thirds of MIS cases were performed by laparoscopy, which reflects the infrequent use of robotic surgery in Europe. All patients underwent surgical treatment with radical hysterectomy, either type B or type C of Querleu and Morrow classification, and bilateral pelvic systematic lymphadenectomy, according to ESGO guidelines in cervical cancer. In 18% of the cases a sentinel lymph node biopsy was performed as well.

In 16.1% of the MIS cases, the surgical procedure included a protective maneuver for the closure of the vagina over the tumor at the time of colpotomy, either at the beginning or at the end of the laparoscopic procedure, to avoid the spillage of the cervical tumor. 58.9% of minimally invasive surgeries were performed with the use of a uterine manipulator.

Intraoperative complications were recorded in 9.6% of the cases, while postoperative complications were registered in 20.9% of the patients. Intraoperative complications included intraoperative bleeding, ureteral or bladder injury, bowel injury and vascular or nerve injury. Postoperative complications included fever and infections, vaginal vault dehiscence or bleeding, lymphatic complications, urinary complications such as haematuria, bladder disfunction, incontinence and urinary fistulas (either bladder or ureteral fistulas), bowel complications as ileum, bowel obstruction, bowel fistulas or leakage, thromboembolic complications.

Table 7. Demographic and surgery-related characteristics of the study population.

Stage IB1 (FIGO 2009) cervical cancer	n=572
Age at surgery (years)	46 (18 – 82)
BMI	25 (15.8 – 68)
PS (ECOG) = 0	519 (93.5%)
Previous conization	171 (29.9%)
Surgical approach • OPEN • MIS → *Laparoscopic* → *Robotic*	 323 (56.5%) 249 (43.5%) *184 (32.1%)* *65 (11.4%)*
Type of hysterectomy • Type B radical hysterectomy • Type C radical hysterectomy	 175 (31.6%) 379 (68.4%)
Sentinel lymph node biopsy	99 (18%)
Number of lymph nodes removed	21 (4 – 76)
Colpo-protective maneuvers	92 (16.1%)
Use of uterine manipulator (in MIS)	133 (58.9%)
Intraoperative complications	54 (9.6%)
Postoperative complications	118 (20.9%)

Legend: Data is expressed as median and range for continuous variables, and absolute number and percentage for categorical variables. BMI=Body Mass Index [weight (kg) / height (m^2)]. PS=Performance Status. ECOG=Easter Cooperative Oncology Group. MIS=Minimally Invasive Surgery.

Pathology report included details about histotype, grading, tumor diameter, the presence of lympho-vascular invasion, the depth of invasion, the number and involvement of the lymph nodes removed (shown in Table 8).

Table 8. Details of pathology reports of the study population.

Histo-pathologic report	
Histotype	
• Squamous carcinoma	396 (69.2%)
• Adenocarcinoma	156 (27.3%)
• Adeno-squamous carcinoma	20 (3.5%)
Grading	
• G1	99 (18.5%)
• G2	259 (48.3%)
• G3	178 (33.2%)
Tumor diameter	20 (0 – 40)
• *<2 cm*	*304 (53.1%)*
• *≥2cm*	*268 (46.9%)*
LVSI	
• Positive	209 (36.5%)
• Negative	363 (63.5%)
Depth of invasion	
• Superficial	198 (34.6%)
• Intermediate	229 (40%)
• Deep	145 (25.4%)
Positive Sedlis criteria	145 (25.3%)
• LVSI +, deep stromal invasion, any tumor diameter	84 (14.7%)
• LVSI +, intermediate stromal invasion, tumor diameter ≥2 cm	61 (10.7%)
Number of lymph nodes removed	21 (4 – 76)
• Left side	10 (2 – 48)
• Right side	11 (1 – 42)

Legend: Data is expressed as median and range for continuous variables, and absolute number and percentage for categorical variables. LVSI=lympho-vascular space invasion

Given the enrolment of IB1 (FIGO 2009) cervical cancer the tumor diameter ranged from 0 to 40 mm, with a median of 20 mm. This parameter was analyzed both as a continuous variable and as discrete variable, hence smaller or larger than 2 cm. This distinction helped to evaluate the importance of the new FIGO 2018 classification, which separates into stages IB1 and IB2 according to tumor diameter <2 cm or ≥2 cm.

Tumor diameter, lympho-vascular invasion and depth of invasion were combined to assess the presence of Sedlis criteria. Sedlis criteria were considered positive in case of deep stromal invasion and lympho-vascular space invasion, regardless of tumor diameter, and in case of intermediate stromal invasion, lympho-vascular space invasion and a tumor diameter larger than 2 cm.

The data reported about histological subtypes and grading mirrored the incidence described in literature.

After examination of the pathology report, in 40.6% of the patients, adjuvant radiation therapy was indicated: 31.5% underwent external beam radiation therapy (EBRT) and 23.8% required brachytherapy, either alone or following EBRT. (Table 8)

In 50 patients, accounting for 8.7% of the study population, concomitant chemotherapy was administered. However, given the stage of the disease included in the study, with the exclusion of patients with nodal metastasis or parametrial involvement, the indication to concomitant chemotherapy remains unclear, as it wasn't specifically reported in the original database.

Table 9. Details of adjuvant treatment administered and oncological outcomes.

Adjuvant treatment and oncological outcomes	
Adjuvant treatment • Radiation therapy - External beam radiation therapy - Brachytherapy *Intracavitary* *Interstitial* • Concomitant chemotherapy	 232 (40.6%) 180 (31.5%) 136 (23.8%) *121 (21.1%)* *16 (2.7%)* 50 (8.7%)
Relapses • *Distant* • *Local* • *Both* • *Unknown*	67 (11.7%) *19 / 67 (28.4%)* *37 / 67 (55.2%)* *8 / 67 (11.9%)* *3 / 67 (4.5%)*
DOD	26 (4.6%)

Legend: Data is expressed as median and range for continuous variables, and absolute number and percentage for categorical variables. DFS=disease-free survival; DOD=death of disease

Relapses were reported in 11.7% of the cases, either as local recurrences, distant dissemination of disease or both; in 3 cases the site of the recurrence was not specified. Within the study population 26 death of disease were reported during the 5-year follow up.

II. STRATIFICATION OF THE POPULATION

Aiming to assess potential predictors of relapse, the study population was stratified, according to the presence of Sedlis criteria and the administration of adjuvant treatment, into 4 groups:

A. Patients who had positive Sedlis criteria and received adjuvant radiation therapy

B. Patients who had positive Sedlis criteria but did not receive adjuvant radiation therapy

C. Patients who had negative Sedlis criteria but received adjuvant radiation therapy

D. Patients who had negative Sedlis criteria and did not receive adjuvant radiation therapy

Table 10. Stratification

		Adjuvant RT	
		Yes	No
Sedlis Criteria	Yes	A N=100	B N=45
	No	C N=132	D N=295

Out of the 572 patients included in the study, 67 patients experienced recurrence. The site of recurrences in the study population is reported in Table 11.

Table 11. Site of relapse in the study population

Relapses	N=67
Distant	19 (28.4%)
Local	37 (55.2%)
Both local and distant	8 (11.9%)
Unknown	3 (4.5%)

Legend: Data is expressed as median and range for continuous variables, and absolute number and percentage for categorical variables.

After stratification of the population in the 4 aforementioned categories, patients in group A experienced relapse in 12% of the cases, 20% in group B, 9.9% in group C and 11.2% in group D (Table 12). In group A, half of the recurrences presented at a distant site and 8.3% of the

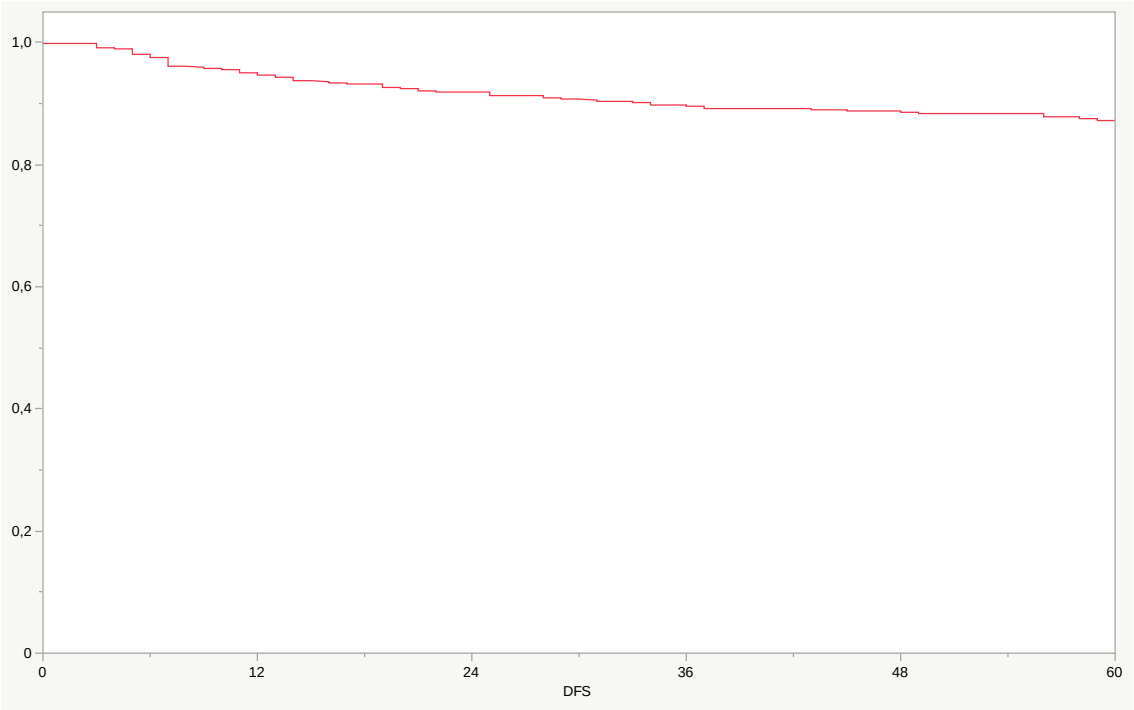
recurrences were both at a local and distant site. In group B, 44.5% of the recurrences were local pelvic relapses, while a third of the recurrences presented as both local and distant. In group C and D, the majority of the relapses were local.

Table 12. Site of relapse by stratification**.**

	A N=100	B N=45	C N=132	D N=295
Relapses	**12 (12%)**	**9 (20%)**	**13 (9.9%)**	**33 (11.2%)**
Distant	6/12(50%)	2/45 (22.2%)	5/132 (45.5%)	6/295 (18.7%)
Local	5 /12(41.7%)	4/45 (44.5%)	6/132 (54.5%)	22/295 (68.8%)
Both local and distant	1/12 (8.3%)	3/45 (33.3%)	0/132 (0%)	4/295 (12.5%)

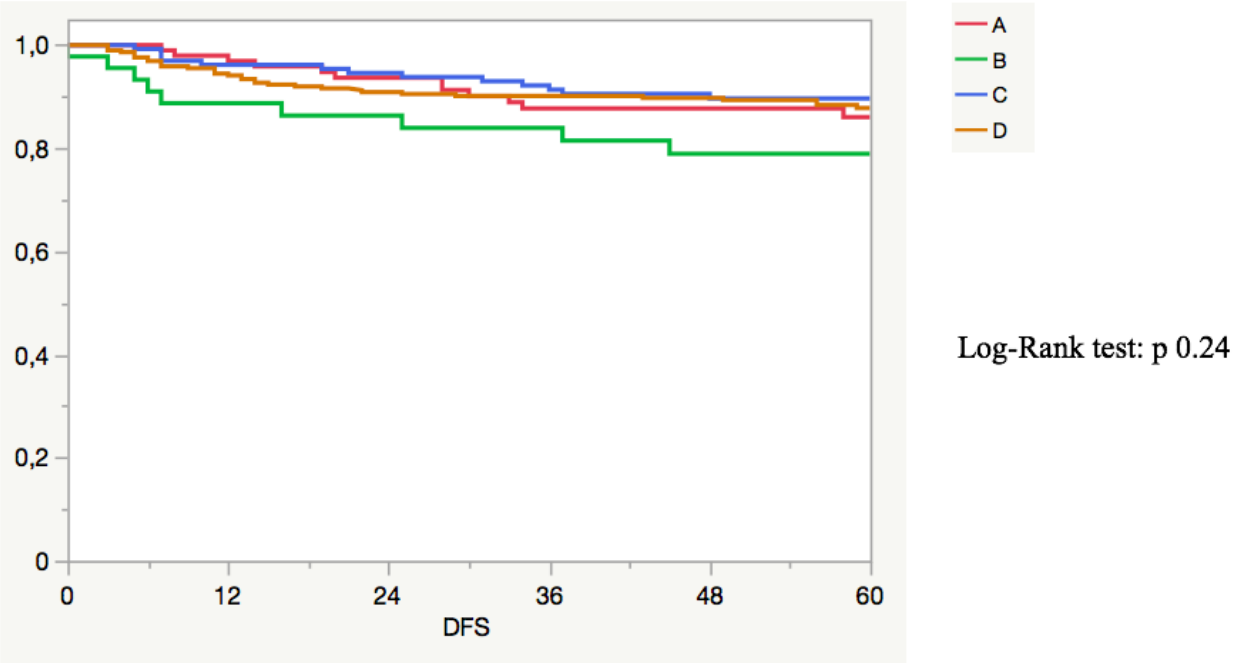
The 5-years DFS reported in literature in localized cervical cancer is 66,7% (10) but it is to be noted that this percentage is calculated including also stages IA1-2. When analyzing stage IB cervical cancer, DFS reported in the literature varies from 80% to 94%. (67) (68) (69) The DFS in the study population is consistent with these data.

Figure 5. DFS in the general population



Even if the limited number of the recurrences do not allow for a statistically significant analysis, the DFS observed by stratification group shows a worse survival trend in patients who had positive Sedlis criteria but did not receive adjuvant radiation therapy (group B), as shown in Figure 6.

Figure 6. DFS by stratification



III. FACTORS INFLUENCING ADJUVANT RADIATION THERAPY

According to international guidelines (18) (20), adjuvant radiotherapy is administered after radical hysterectomy depending on surgical findings and pathologic stage of the disease. The main indications to postoperative radiation therapy are commonly referred to as Sedlis criteria. However, potential risk factors for recurrence may not only be limited to these criteria, and additional risk factor may be taken into account when counselling a patient for adjuvant treatment, such as histology (e.g. adenocarcinoma) or close or positive surgical margins. Moreover, even in the presence of Sedlis criteria, if the surgical procedure performed is deemed appropriate, observation may be an alternative option, especially in experienced centers.

In this setting, we conducted an analysis aimed to evaluate which parameters induced clinicians to indicate postoperative radiation therapy.

We first conducted a univariate analysis investigating the potential role of baseline patient's characteristics as well as surgical and pathological findings (reported in Table 13). At this evaluation many factors emerged as elements influencing the administration of adjuvant radiotherapy.

Age of the patient at the time of surgery influenced postoperative radiotherapy, and patients older than 50 years were more likely to undergo adjuvant treatment. Other patient's characteristics such as BMI or performance status did not influence clinicians' choice.

The surgical approach chosen for radical hysterectomy was significantly related to indication to adjuvant radiation therapy: patients treated with open surgery were more likely to undergo postoperative treatment than patients treated with MIS, either with laparoscopic or robotic surgery. The type of hysterectomy performed, the use of protective maneuvers and intraoperative complications were not implicated in the choice of postoperative therapy. The number of lymph nodes removed in the pelvic systematic lymphadenectomy was significantly related to indication to

adjuvant treatment, while sentinel lymph node biopsy did not play a role. If the lymphadenectomy performed was not deemed adequate, patients were more likely to be subjected to postoperative radiation therapy.

Considering pathologic findings, out analysis confirmed the relevance of Sedlis criteria, as tumor diameter, depth of invasion and lympho-vascular space invasion were all significantly related to adjuvant treatment, either considered alone or in combination. Moreover, grading and histology emerged as factors significantly influencing postoperative treatment.

To eliminate potential confounders, we also conducted a multivariate analysis considering multiple anamnestic, surgical and pathological elements, with a clinical relevance to adjuvant treatment. This analysis once again confirmed the role of Sedlis criteria, as tumor diameter, depth of invasion and lympho-vascular space invasion all resulted significantly related to the indication to postoperative radiotherapy.

In particular, the subgroup of patient with tumors greater than 2 cm were more likely to be treated with adjuvant radiotherapy (OR 1.7; 95% CI, 1.02 to 2.88, p 0.04) and patients with positive LVSI were twice more likely to undergo postoperative treatment (OR 2.05; 95% CI 1.24 to 3.39, p 0.004).

Depth of invasion was a fundamental factor impacting on indication to adjuvant radiation therapy: the possibility of undergoing postoperative treatment was respectively 5 times (OR 5.11; 95% CI, 2.43 to 10.74; p <0.001) and almost 2 times (OR 1.97; 95% CI, 1.10 to 3.55, p 0.02) higher in patients with deep stromal invasion compared to those with superficial and intermediate stromal invasion.

Moreover, with respect to the univariate analysis, the only other factor who maintained its relevance was surgical approach: patients who underwent open surgery were twice more likely to be

administered adjuvant radiation therapy (OR 2.32, 95% CI 1.19 to 4.51, p 0.01). Protective maneuvers did not influence postoperative treatment.

Table 13. Analysis of the factors influencing adjuvant radiotherapy.

	Univariate Analysis			Multivariate Analysis	
	Adjuvant RT: No (n=340)	Adjuvant RT: Yes (n=232)	P value	Odds Ratio (95% CI)	P value
Age at surgery (years)	45 (18 – 82)	48 (24 – 82)	**0.002**		
→ *>50 years*	*121 (35.6%)*	*105 (45.3%)*	**0.02**	1.01 (0.62 – 1.65)	0.94
BMI (kg/m2)	24 (15.8 – 68)	25 (17 – 46)	0.08		
→ *BMI >25.5*	*115 (40.8%)*	*94 (47.2%)*	0.16	1.37 (0.84 – 2.22)	0.2
Performance Status					
• PS=0	307 (94.2%)	212 (92.6%)	0.48	0.7 (0.47 – 1.81)	0.47
• PS>0	19 (5.8%)	17 (7.4%)			
Previous conization	112 (32.9%)	59 (25.4%)	0.06		
Surgical approach					
• OPEN	170 (50%)	153 (66%)	**<0.001**	2.32 (1.19 – 4.51)	**0.01**
• MIS	170 (50%)	79 (34%)			
- *Laparoscopic*	*121 (35.6%)*	*63 (27.1%)*			
- *Robotic*	*49 (14.4%)*	*16 (6.9)*			
Use of uterine manipulator in MIS	87/170 (51.1%)	46/79 (58.2%)	0.95	2.1 (0.97 – 4.54)	0.05
Colpo-protective maneuvers	53 (15.6%)	39 (16.8%)	0.69	0.89 (0.46 – 1.73)	0.73
Type of hysterectomy			0.64	0.93 (0.58 – 1.66)	0.95
• Type B radical hysterectomy	106 (32.4%)	69 (30.4%)			
• Type C radical hysterectomy	221 (67.6%)	158 (69.6%)			
Intraoperative complications	34 (10.2%)	20 (8.7%)	0.66	1.09 (0.48- 2.51)	0.82
Histology			**0.02**		
• Squamous carcinoma (1)	221 (65%)	175 (75.4%)		(1) vs (2): 1.23 (0.71-2.15)	0.44
• Adenocarcinoma (2)	106(31.2%)	50 (21.6%)		(1) vs (3): 1.83 (0.54-6.12)	0.32
• Adenosquamous carcinoma (3)	13 (3.8%)	7 (3%)			
Tumor diameter (mm)	16 (0 – 40)	25 (0 – 40)	**<0.001**		
Tumor diameter				1.7 (1.02 – 2.88)	**0.04**
• <2 cm	219 (64.4%)	85 (36.6%)	**<0.001**		
• ≥2cm	121 (35.6%)	147 (63.4%)			
Grading			**<0.001**		
• G1	76 (23.8%)	23 (10.6%)		G3 vs G1: 1.04 (0.48-2.27)	0.90
• G2	152 (47.7%)	107 (49.3%)		G3 vs G2: 1.35 (0.80-2.28)	0.25
• G3	91 (28.5%)	87 (40.1%)			
LVSI	88 (25.9%)	121 (52.2%)	**<0.001**	2.05 (1.24 – 3.39)	**0.004**
Depth of invasion			**<0.001**		
• Superficial (1)	115 (45.6%)	43 (18.5%)		(3) vs (1): 5.11 (2.43-10.74)	**<0.001**
• Intermediate (2)	132 (38.8%)	97 (41.8%)		(3) vs (2): 1.97 (1.10-3.55)	**0.02**
• Deep (3)	53 (15.6%)	92 (39.7%)			
Sedlis criteria			**<0.001**		
• Negative	295 (86.8%)	132 (56.9%)			
• Positive	45 (13.2%)	100 (43.1%)			
Sentinel lymph node biopsy	63 (19.4%)	36 (16.1%)	0.36	0.54 (0.27 – 1.06)	0.07
Number of lymph nodes removed	22 (5 – 76)	20 (4 – 58)	**<0.001**		
Postoperative complications	70 (20.8%)	48 (21.1%)	1	0.94 (0.52 – 1.69)	0.85
→ *Urinary or bowel fistulas*	12 (3.5%)	4 (1.7%)	0.3		

Legend: Data is expressed as median and range for continuous variables and absolute number and percentage for categorical variables.

IV. FACTORS INFLUENCING RECURRENT DISEASE

Aiming to investigate potential risk factors other than Sedlis criteria, we conducted a further analysis on factors associated with recurrence in our population.

Analogously to the precedent evaluation, the role of baseline patient's characteristics as well as surgical and pathological findings was investigated. We created two models to evaluate these risk factors: in Model 1 tumor diameter, depth of invasion and lympho-vascular space invasion were considered as single variables potentially influencing the risk of recurrence, while in Model 2 they were combined in a single variable as Sedlis criteria.

1. Model 1: Sedlis criteria as separate variables

The findings of the Model 1 are presented in Table 14. In the univariate analysis, the precedent conization procedure appeared to have a potential protective effect against relapse, while no other baseline patient characteristics exhibited a statistically significant association with recurrent disease. Consistent with the outcomes of the original SUCCOR trial, wherein patients who underwent minimally invasive surgery faced twice the risk of recurrence compared to those who underwent open surgery, we observed a significant link between minimally invasive surgery (MIS) and an elevated risk of relapse. The utilization of a uterine manipulator, among protective measures, was associated with an unfavorable outcome and an increased risk of relapse. In contrast to the SUCCOR trial's findings, in our study population, colpo-protective measures did not exert a significant influence on survival.

When considering tumor diameter, depth of invasion, and lympho-vascular space invasion (LVSI) as individual variables, only tumor diameter emerged as significantly related to recurrence, with tumors larger than 2 cm exhibiting a substantially elevated risk of recurrence. Conversely, lympho-vascular space invasion and depth of invasion did not demonstrate a statistically significant association with recurrence.

Given the incidence of recurrence in our study population, we conducted a multivariate analysis encompassing the seven factors that were deemed clinically most relevant. In addition to the obvious factors such as tumor diameter, depth of invasion, and LVSI, we also considered age at surgery, surgical approach, tumor grading, and adjuvant therapy. Among these factors, only a tumor diameter exceeding 2 cm was found to be significantly linked to an increased risk of recurrence (OR 1.26; 95% CI 1.03 to 1.54, $p < 0.02$).

Table 14. Model 1: Analysis of the factors influencing recurrent disease (Sedlis criteria as separate variables).

	Univariate Analysis			Multivariate Analysis	
	Relapse: No (n=505)	Relapse: Yes (n=67)	P value	Odds Ratio (95% CI)	P value
Age at surgery (years)	46 (18 – 82)	49 (28 – 82)	0.06		
→ *>50 years*	*194 (38.4%)*	*32 (47.8%)*	*0.14*	1 (0.83-1.21)	0.92
BMI (kg/m2)	25 (15.8 – 68)	25 (19 – 40)	0.62		
→ *BMI >25.5*	*185 (44%)*	*24 (39.4%)*	*0.58*		
Performance Status					
• PS=0	459 (93.7%)	60 (92.3%)	0.59		
• PS>0	31 (6.3%)	5 (7.8%)			
Previous conization	162 (32.1%)	9 (13.4%)	**0.001**		
Surgical approach					
• OPEN	299 (59.2%)	24 (35.8%)	**<0.001**	1.1 (0.91-1.33)	0.29
• MIS	206 (40.8%)	43 (64.2%)			
- *Laparoscopic*	*152 (30.1%)*	*32 (47.8%)*			
- *Robotic*	*54 (10.7%)*	*11 (16.4%)*			
Use of uterine manipulator	104/206 (50.5%)	29/43 (67.4%)	**<0.001**		
Colpo-protective maneuvers	82 (16.2%)	10 (14.9%)	0.47		
Type of hysterectomy			0.08		
• Type B radical hysterectomy	149 (30.3%)	26 (41.9%)			
• Type C radical hysterectomy	343 (69.7%)	36 (58.1%)			
Intraoperative complications	50 (10%)	4 (6.2%)	0.38		
Histology			**0.04**		
• Squamous carcinoma (1)	352 (69.7%)	44 (65.7%)			
• Adenocarcinoma (2)	133 (26.3%)	23 (34.3%)			
• Adenosquamous carcinoma (3)	20 (4%)	0 (0%)			
Tumor diameter (mm)	20 (0 – 40)	25 (0 – 40)	**0.006**		
Tumor diameter			**0.006**	1.26 (1.03-1.54)	**0.02**
• <2 cm	279 (55.3%)	25 (37.3%)			
• ≥2cm	226 (44.7%)	42 (62.7%)			
Grading			0.06		
• G1	93 (19.7%)	6 (9.4%)		G3 vs G1-2: 1.02 (0.83-1.25)	0.82
• G2	228 (48.3%)	31 (48.4%)			
• G3	151 (32%)	27 (42.2%)			
LVSI	183 (36.2%)	26 (38.8%)	0.68	1.09 (0.89-1.34)	0.37
Depth of invasion			0.05		
• Superficial (1)	182 (36%)	16 (23.9%)		(3) vs (1): 0.84 (0.63-1.11)	0.24
• Intermediate (2)	202 (40%)	27 (40.3%)		(3) vs (2): 0.81 (0.64-1.04)	0.10
• Deep (3)	121 (24%)	24 (35.8%)			
Sedlis criteria			0.23		
• Negative	381 (75.4%)	46 (68.7%)			
• Positive	124 (24.6%)	21 (31.3%)			
- *LVSI+, deep stromal invasion*	*71 (14.1%)*	*13 (19.4%)*	0.26		
- *LVSI+, intermediate stromal invasion, ≥2cm*	*59 (88.1%)*	*8 (11.9%)*	0.67		
Sentinel lymph node biopsy	83 (17.2%)	16 (24.2%)	0.17		
Number of lymph nodes removed	21 (4 – 76)	23 (7 – 59)	0.81		
Postoperative complications	108 (21.7%)	10 (14.9%)	0.26		
→ *Urinary or bowel fistulas*	14 (2.8%)	2 (3%)	1		
Adjuvant RT	207 (41%)	25 (37.3%)	0.59	0.92 (0.75-1.13)	0.47
• EBRT	165 (32.7%)	15 (22.4%)	0.09		
• Brachytherapy	120 (23.8%)	16 (23.9%)	1		

Legend: Data is expressed as median and range for continuous variables and absolute number and percentage for categorical variables.

2. Model 2: Sedlis criteria as a single variable

A second analysis was conducted considering tumor diameter, LVSI and depth of invasion combined as a single variable: positive or negative Sedlis criteria. Sedlis criteria were considered positive in the presence of lympho-vascular space invasion associated with deep stromal invasion, regardless of tumor size, or in the presence of lympho-vascular space invasion associated with intermediate stromal invasion and a tumor larger than 2 cm.

Factors considered in the multivariate analysis were age at surgery, surgical approach, grading, Sedlis criteria, adjuvant treatment and sentinel lymph node biopsy. The results are shown in Table 15.

Among the elements considered, the only statistically significant factor associated with the risk of relapse was the surgical approach to radical hysterectomy. Once again, the results of the SUCCOR trial (and the LACC trial) were confirmed, and MIS associated with worse oncological outcomes than open surgery. In detail, in patients treated with MIS, either with laparoscopy or robotic surgery, the risk of recurrence was more than double that of patients who underwent open radical hysterectomy (OR 2.65; 95% CI 1.53 to 4.57, p <0.001).

The presence of positive Sedlis criteria appeared to be associated with higher rates of recurrence, even if the correlation did not reach statistical significance (p 0.06).

Table 15. Model 2: Analysis of the factors influencing recurrent disease (Sedlis criteria as a single variable).

	Univariate Analysis			Multivariate Analysis	
	Relapse: No (n=505)	Relapse: Yes (n=67)	P value	Odds Ratio (95% CI)	P value
Age at surgery (years)	46 (18 – 82)	49 (28 – 82)	0.06		
→ *>50 years*	*194 (38.4%)*	*32 (47.8%)*	*0.14*	1.52 (0.92 – 2.50)	0.09
BMI (kg/m2)	25 (15.8 – 68)	25 (19 – 40)	0.62		
→ *BMI >25.5*	*185 (44%)*	*24 (39.4%)*	*0.58*		
Performance Status					
• PS=0	459 (93.7%)	60 (92.3%)	0.59		
• PS>0	31 (6.3%)	5 (7.8%)			
Previous conization	162 (32.1%)	9 (13.4%)	**0.001**		
Surgical approach					
• OPEN	299 (59.2%)	24 (35.8%)	**<0.001**	2.65 (1.53 – 4.57)	**<0.001**
• MIS	206 (40.8%)	43 (64.2%)			
- *Laparoscopic*	*152 (30.1%)*	*32 (47.8%)*			
- *Robotic*	*54 (10.7%)*	*11 (16.4%)*			
Use of uterine manipulator	104/206 (50.5%)	29/43 (67.4%)	**<0.001**		
Colpo-protective maneuvers	82 (16.2%)	10 (14.9%)	0.47		
Type of hysterectomy			0.08		
• Type B radical hysterectomy	149 (30.3%)	26 (41.9%)			
• Type C radical hysterectomy	343 (69.7%)	36 (58.1%)			
Intraoperative complications	50 (10%)	4 (6.2%)	0.38		
Histology			**0.04**		
• Squamous carcinoma (1)	352 (69.7%)	44 (65.7%)			
• Adenocarcinoma (2)	133 (26.3%)	23 (34.3%)			
• Adenosquamous carcinoma (3)	20 (4%)	0 (0%)			
Tumor diameter (mm)	20 (0 – 40)	25 (0 – 40)	**0.006**		
Tumor diameter					
• <2 cm	279 (55,3%)	25 (37,3%)	**0.006**		
• ≥2cm	226 (44,7%)	42 (62,7%)			
Grading			0.06		
• G1	93 (19.7%)	6 (9.4%)		G3 vs G1-2: 1.42 (0.85-2.37)	0.16
• G2	228 (48.3%)	31 (48.4%)			
• G3	151 (32%)	27 (42.2%)			
LVSI	183 (36.2%)	26 (38.8%)	0.68		
Depth of invasion			0.05		
• Superficial (1)	182 (36%)	16 (23.9%)			
• Intermediate (2)	202 (40%)	27 (40.3%)			
• Deep (3)	121 (24%)	24 (35.8%)			
Sedlis criteria			0.23	1.74 (0.96 – 3.12)	0.06
• Negative	381 (75.4%)	46 (68.7%)			
• Positive	124 (24.6%)	21 (31.3%)			
- *LVSI+, deep stromal invasion*	*71 (14.1%)*	*13 (19.4%)*	0.26		
- *LVSI+, intermediate stromal invasion, ≥2cm*	*59 (88.1%)*	*8 (11.9%)*	0.67		
Sentinel lymph node biopsy	83 (17.2%)	16 (24.2%)	0.17	1.06 (0.58 – 1.94)	0.82
Number of lymph nodes removed	21 (4 – 76)	23 (7 – 59)	0.81		
Postoperative complications	108 (21.7%)	10 (14.9%)	0.26		
→ *Urinary or bowel fistulas*	14 (2.8%)	2 (3%)	1		
Adjuvant RT	207 (41%)	25 (37.3%)	0.59	0.76 (0.43 – 1.33)	0.34
• EBRT	165 (32.7%)	15 (22.4%)	0.09		
• Brachytherapy	120 (23.8%)	16 (23.9%)	1		

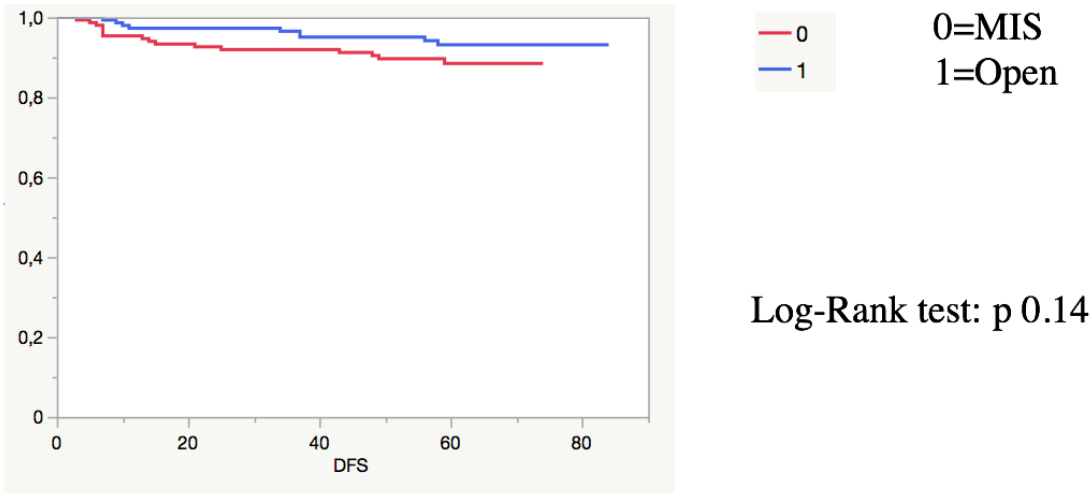
Legend: Data is expressed as median and range for continuous variables and absolute number and percentage for categorical variables.

3. Survival analysis

As established by prior research findings and our own analysis (48, 56), it is well-documented that the choice of surgical approach has a substantial influence on the risk of recurrence in cervical cancer. Notably, minimally invasive surgery (MIS) has been consistently associated with a notably poorer oncological prognosis in this context. In line with the methodology applied in the initial SUCCOR trial's survival analysis, we conducted a similar assessment of disease-free survival within our study population, stratifying it into two subgroups based on tumor diameter.

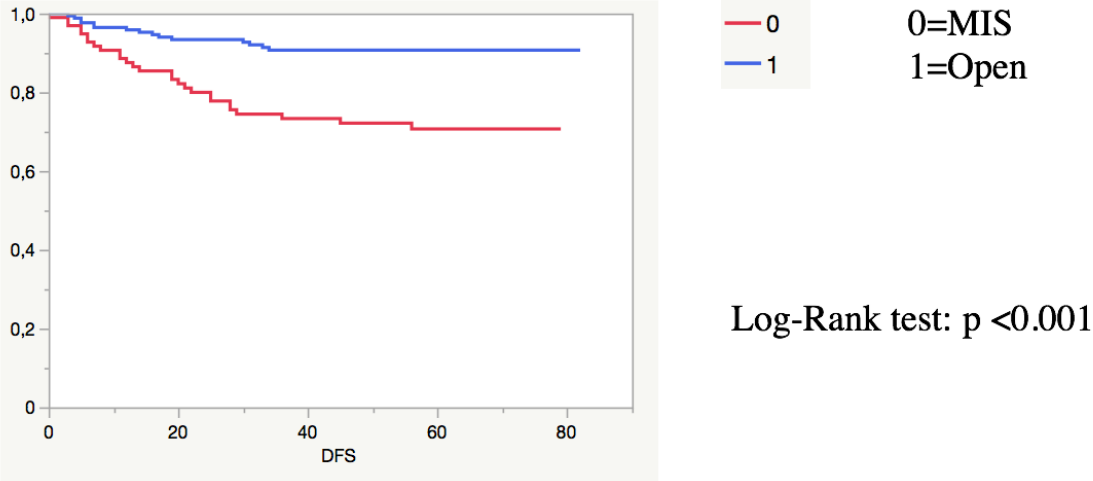
Within the subgroup of patients with tumors measuring less than 2 cm, our investigation did not reveal any significant disparity in disease-free survival between the open surgery group and the MIS group (see Figure 7).

Figure 7. DFS in patients with tumors <2 cm according to surgical approach



In the subgroup of patients with tumors larger than 2 cm, on the contrary, survival was significantly influenced by surgical approach and patients treated with MIS had a significantly higher risk of recurrence than the open surgery group (Figure 8.)

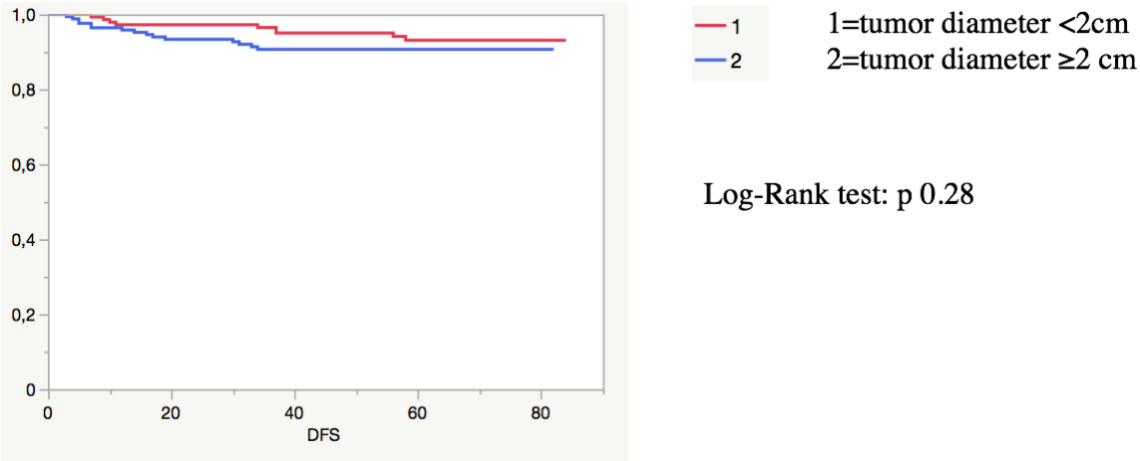
Figure 8. DFS in patients with tumors ≥2 cm according to surgical approach



Secondarily, we conducted a survival analysis dividing our population in two groups according to the surgical approach.

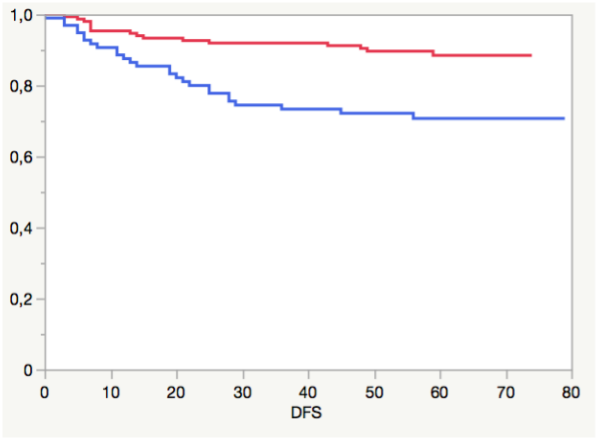
In the open surgery group, DFS did not differ according to tumor diameter, as shown in Figure 9.

Figure 9. DFS in patients treated with OPEN surgery according to tumor diameter



Conversely, within the MIS group, tumor diameter larger than 2 cm was significantly related to a lower DFS and a higher risk of recurrence, compared to smaller tumors.

Figure 10. DFS in patients treated with MIS according to tumor diameter



V.FACTORS INFLUENCING RECURRENT DISEASE IN PATIENTS WHO DID NOT RECEIVE ADJUVANT THERAPY

Lastly, our study sought to assess the potential beneficiaries of adjuvant treatment and carried out an analysis of risk factors associated with recurrent disease in a cohort of patients who did not receive postoperative radiation therapy. The findings within this subset of patients were consistent with those observed in the broader study population, except for the protective effect of prior conization against relapse, which was unique. Other patient characteristics did not exhibit significant associations with recurrent disease.

As anticipated, within this specific subgroup, minimally invasive surgery (MIS) demonstrated a statistically significant correlation with an increased risk of recurrence, while the use of a uterine manipulator was associated with a less favorable prognosis. Among the pathological factors considered, tumor diameter emerged as the sole variable significantly linked to relapse, with tumors larger than 2 cm carrying a substantially elevated risk of recurrence.

Subsequent multivariable analysis, which factored in surgical approach and the three parameters outlined in the Sedlis criteria, identified minimally invasive surgery and tumor diameter as the primary factors significantly connected to recurrence.

Notably, in this particular population, minimally invasive surgery exhibited a nearly threefold greater risk of recurrence compared to open surgery (OR 2.89; 95% CI 1.47 to 5.66, $p < 0.01$). Additionally, patients with tumor diameters exceeding 2 cm who did not receive radiation therapy faced a nearly threefold higher risk of recurrence compared to their counterparts with smaller tumors following the same treatment pathway (OR 2.9; 95% CI 1.49 to 5.63, $p < 0.01$).

Table 16. Analysis of the factors influencing recurrent disease in patients who did not receive adjuvant radiotherapy (n=340)

	Univariate Analysis			Multivariate Analysis	
	Relapse: No (n=298)	Relapse: Yes (n=42)	P value	Odds Ratio (95% CI)	P value
Age at surgery (years) → *>50 years*	45 (18 – 82) *102 (34.2%)*	47 (28 – 66) *19 (45.2%)*	0.12 *0.17*		
BMI (kg/m2) → *BMI >25.5*	24.3 (15.8 – 68) *101 (41.4%)*	23.7 (19 – 36) *14 (36.8%)*	0.27 *0.72*		
Performance Status • PS=0 • PS>0	 270 (94.4%) 16 (5.6%)	 37 (92.5%) 3 (7.5%)	0.71		
Previous conization	106 (35.6%)	6 (14.3%)	**0.005**		
Surgical approach • OPEN • MIS - *Laparoscopic* - *Robotic*	 157 (52.7%) 141 (47.3%) *102 (34.2%)* *39 (13.1%)*	 13 (31%) 29 (69%) *19 (45.2%)* *10 (23.8%)*	 **0.01**	 2.89 (1.47 – 5.66)	 **0.01**
Use of uterine manipulator	69/141 (48.9%)	18/29 (62%)	**0.006**		
Colpo-protective maneuvers	44 (14.8%)	9 (21.4%)	0.26		
Type of hysterectomy • Type B radical hysterectomy • Type C radical hysterectomy	 93 (32.2%) 196 (67.8%)	 13 (34.2%) 25 (65.8%)	 0.85		
Intraoperative complications	33 (11.3%)	1 (2.4%)	0.09		
Histology • Squamous carcinoma (1) • Adenocarcinoma (2) • Adenosquamous carcinoma (3)	 196 (65.8%) 89 (29.9%) 13 (4.3%)	 25 (59.5%) 17 (40.5%) 0 (05)	 0.18		
Tumor diameter (mm)	15 (0 – 40)	22 (0 – 40)	**0.001**		
Tumor diameter • <2 cm • ≥2cm	 202 (67.8%) 96 (32.2%)	 17 (40.5%) 25 (59.5%)	 **<0.001**	 2.9 (1.49 – 5.63)	 **0.01**
Grading • G1 • G2 • G3	 70 (25.2%) 132 (47.3%) 77 (27.6%)	 6 (15%) 20 (50 %) 14 (35%)	 0.32		
LVSI	75 (25.2%)	13 (31%)	0.45	1.24 (0.61 – 2.51)	0.54
Depth of invasion • Superficial (1) • Intermediate (2) • Deep (3)	 141 (47.3%) 115 (38.6%) 42 (14.1%)	 14 (33.3%) 17 (40.5%) 11 (26.2%)	 0.07	 (3) vs (1): 1.69 (0.68-1.13) (3) vs (2): 1.37 (0.61-3.03)	 0.25 0.43
Sedlis criteria • Negative • Positive - *LVSI+, deep stromal invasion* - *LVSI+, intermediate stromal invasion, ≥2cm*	 262 (87.9%) 36 (12.2%) *20 (6.7%)* *16 (5.4%)*	 33 (78.5%) 9 (21.5%) *7 (16.7%)* *2 (4.8%)*	 *0.05* *1*		
Sentinel lymph node biopsy	50 (17.6%)	13 (31.7%)	0.05		
Number of lymph nodes removed	21.5 (5 – 76)	23.5 (9 – 59)	0.56		
Postoperative complications	63 (21.4%)	7 (16.7%)	0.54		

DISCUSSION

The postoperative management of cervical cancer remains a subject of extensive discussion, guided by the identification of pivotal risk factors and diligent consideration of a patient's unique clinical profile. The so-called Sedlis criteria, introduced in 1999 by Sedlis, have significantly influenced the administration of adjuvant therapy in stage IB cervical cancer. This approach focused on the combination of three key risk factors: tumor size, lympho-vascular space invasion (LVSI), and depth of stromal invasion, providing a valuable framework for risk assessment and therapeutic decision-making (Sedlis, 1999) (58). Nonetheless, international guidelines, while appreciating the utility of the Sedlis criteria, have also recognized that additional clinical elements and patient-specific characteristics may exert influence in this intricate decision-making process. Consequently, the ultimate choice for adjuvant therapy often remains at the discretion of the treating clinician, who takes into account a comprehensive evaluation of the patient's characteristics and any potential risk factors for recurrence.

The primary objective of our study was to scrutinize which parameters, apart from the Sedlis criteria, were of significance in the European context when it came to indicating postoperative radiotherapy. In our comprehensive population, the relevance of the Sedlis criteria was reaffirmed, as parameters including tumor diameter, LVSI, and depth of invasion all demonstrated a significant relationship with the administration of postoperative radiotherapy. Notably, we unveiled that the surgical approach chosen for radical hysterectomy was an influential factor that significantly correlated with the need for adjuvant treatment. Specifically, patients undergoing open surgery were more prone to require postoperative radiotherapy.

An important caveat to consider is the potential bias in this regard, linked to the selective nature of the patient population. As reported in the SUCCOR trial, patients treated with minimally invasive surgery often presented with more favorable prognostic features, including smaller tumor sizes.

Nevertheless, even after conducting a multivariate analysis to eliminate potential confounders, patients treated with open surgical approaches continued to receive adjuvant therapy at higher rates. One plausible explanation may reside in the patient selection process for open surgery, whereby patients with additional risk factors, distinct from those considered in our analysis, were deemed at higher risk of recurrence and therefore recommended for adjuvant radiotherapy.

The regional variation in healthcare systems also emerged as a consideration, as it can significantly affect the choice of surgical approach and the subsequent indications for adjuvant therapy (70). These choices may be influenced by cultural and sociodemographic differences among various countries. The wide range of centers and countries contributing to our original dataset made it challenging to standardize and adjust for these regional differences fully.

After segmenting our population based on the presence of the Sedlis criteria and the administration of adjuvant radiotherapy, we shifted our focus to assessing the recurrence rates within these subgroups. Strikingly, we discovered a notable recurrence rate among patients who did not meet the Sedlis criteria, even when they underwent adjuvant radiotherapy. This rate closely resembled that observed in patients presenting known risk factors for recurrence. Consequently, we felt it was imperative to explore which patients could derive the most substantial benefit from adjuvant radiation therapy. To achieve this, we delved into the factors associated with recurrence, both within the entire population and within the subgroup of patients who did not receive adjuvant therapy.

Our study uncovered that the choice of surgical approach emerged as the primary factor impacting survival when considering the Sedlis criteria as a singular parameter. However, upon conducting a more detailed analysis that considered the individual influence of each risk factor, tumor diameter stood out as the sole factor significantly affecting survival in appropriately staged, node-negative IB cervical cancer. Notably, larger tumors exhibited significantly worse prognoses, particularly in the

minimally invasive surgery group. In contrast, no significant link between the surgical approach and disease-free survival was observed in patients with smaller tumors, aligning with findings from the SUCCOR trial. In the case of open surgery, it was effective in nullifying survival disparities dependent on tumor diameter.

Although both the LACC trial and Melamed's study (48) (47) did not demonstrate statistically significant differences in survival among a subgroup of patients with tumors smaller than 2 cm, it is important to acknowledge that these studies were not powered to address this specific aspect. An investigation by Casarin et al. identified tumor size and the presence of residual tumor at the time of surgery as the primary independent predictors of recurrence in patients who underwent laparoscopic radical hysterectomy for early-stage cervical cancer. Interestingly, preoperative conization with free margins emerged as a protective factor, significantly reducing the risk of recurrence (71).

In light of these findings, the most recent ESGO guidelines for cervical cancer, issued in 2022, have introduced the possibility of opting for minimally invasive surgery in selected cases, following thorough patient counseling. These cases are specifically defined as tumors smaller than 2 cm with free margins after conization, to be performed in high-volume centers experienced in minimally invasive surgery (72).

It has to be noted that our study carries certain limitations inherent to its retrospective observational nature. However, the strength of our findings is bolstered by the robust methodology of data collection carried out by the SUCCOR study group, which assembled a vast database of patients undergoing radical hysterectomy for IB1 cervical cancer in a European context. Although our research may serve as valuable preliminary evidence, the potential for further validation of these findings remains, and it could be pursued through prospective trials. The rationale for launching such a trial in the post-LACC era, where the superiority of open surgery has been affirmed, may be subject to debate.

Nonetheless, as the data from the LACC trial and the SUCCOR trial predominantly stem from an analysis that focused on laparoscopy as a form of minimally invasive surgery, it is noteworthy that two separate investigations are currently underway to explore the role of robotic surgery in cervical cancer patients. The RACC trial, a multicenter prospective randomized trial in Sweden, is investigating the impact of robotic surgery on disease-free survival and overall survival (73). In China, a similar trial is in progress, with a subgroup analysis examining patients with tumors smaller than 2 cm (74). These forthcoming results may offer further insights into the influence of surgical approach on disease-free survival and the potential role of minimally invasive surgery in managing small tumors.

In conclusion, the strength of our analysis lies in the meticulous data collection process carried out by the SUCCOR study group, which successfully brought together contributions from numerous centers across European countries. Despite the retrospective nature of our study, the comprehensive approach to data collection has helped mitigate the inherent biases. In conclusion, our study sheds light on the association between surgical approach, the Sedlis criteria, and survival in the context of radical hysterectomy for IB1 cervical cancer. It has reaffirmed the protective effect of open surgery and underscored the pivotal role of tumor diameter as a risk factor for recurrence, regardless of the use of adjuvant radiation therapy. The findings also underscore the need for continued research to refine the indications for postoperative therapy, ensuring that adjuvant treatments are optimally targeted to those who stand to benefit most.

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