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WIDE LOCAL EXCISION VS MOHS TÜBINGEN TECHNIQUE IN THE TREATMENT OF DERMATOFIBROSARCOMA PROTUBERANS: A TWO- CENTRE RETROSPECTIVE STUDY AND LITERATURE REVIEW.

RUNNING HEAD: DFSP TREATMENT: A RETROSPECTIVE STUDY AND LITERATURE REVIEW

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ABSTRACT

Background: Dermatofibrosarcoma Protuberans is a rare, low-grade mesenchymal skin tumour, characterized by slow infiltrative growth and common local recurrence, with infrequent distant metastases.

Objective: The aim of this study is to better clarify clinico-pathological characteristics of this tumour and to evaluate the cure rates of Mohs Tübingen technique (MTT) and wide local excision. Eventually, we perform a literature review to compare our experience with published data.

Methods: A retrospective review was conducted on 135 patients diagnosed, treated and followed-up between 1997 and 2014 at two different institutions. Sixty-two patients underwent to wide local excision and 73 to MTT. The primary end-points were: percentage of recurrences, time-to-progression and recurrence annual risk rate. Then, the PubMed database was searched for Dermatofibrosarcoma Protuberans case series treated with standard surgical resection, wide local excision, Mohs micrographic surgery and MTT. The annual risk rate of recurrence calculated and reported for the four separate procedures, was pooled to compare them.

Results: Five out the 62 patients with wide local excision (8.1%) experienced recurrences after a mean follow-up of 4.7 years; the percentage of recurred patients 9 years after MTT was 5.5%, and the annual recurrence risk rate of 0.6%. Pooling these data with those from literature, the recurrence rate varies from 26% to 60% for standard surgical resection, from 0 and 41% for wide local excision, from 0 and 8,3% for Mohs micrographic surgery and from 0 to 5.5%. for MTT. The lowest annual recurrence risk rate was found for MTT.

Conclusion: Significantly lower recurrence rates were recorded in patients treated with classic or Tübingen Mohs technique. To the best of our knowledge, our case series is the widest treated with MTT ever described in the literature; these data may be useful to guide clinicians in the choice of the gold standard treatment for Dermatofibrosarcoma Protuberans.

INTRODUCTION

Dermatofibrosarcoma Protuberans (DFSP) is a rare, low-grade mesenchymal skin tumour, that was first described by Darier and Ferrand in 1924[1-4], even if the currently accepted term was coined by Hoffman in 1925[5]. Its estimated incidence is 0,8-5 cases per million a year[6,7], greater in black race[7,8], with a male-female ratio of 1:1[1,9-11]. Median age at diagnosis is 20-59 years[1], however, congenital and paediatric cases have also been described[2,12,13-16].

As for all soft tissue sarcomas, DFSP has no specific risk factors; it arises generally on healthy skin but occasionally can develop on chronically damaged areas[5,16]. Despite its rapid progression during pregnancy, it's not demonstrated an eventually hormonal origin[17].

The malignant potential of DFSP is considered as intermediate between that of dermatofibroma and malignant fibrous histiocytoma[18].

The main cytogenetical features of this tumour is represented by supernumerary ring chromosomes derived from t(17;22) or, more uncommonly, reciprocal translocation t(17;22)(q22;q13)[19], featured in more than 90% of DFSP[20]. This biological mechanism justifies the use of tyrosine kinase inhibitors in the DFSP treatment[21-24].

The tumour is characterized by a progressive, locally infiltrative growth and if left untreated, shows a slow and locally infiltrative invasiveness of surrounding tissue, such as fat, fascia, muscle and periosteum as well as neurovascular bundles. The subclinical extension of DFSP is highly unpredictable and can vary from 0.3 cm. to 12 cm. over the macroscopic borders[25]. These irregular extensions can cause uncertainty in determining clean excision margins, and may result in the high risk of local recurrence[26].

Metastasis are rare and mainly localized in regional lymph node or distantly in the lung; in many cases were preceded by multiple local recurrences[5].

Gold standard treatment of the tumour is represented by complete surgical excision, with a recurrence rate variable from 26 to 60% for standard surgical resection (SSR), from 0 to 41% for wide local excision (WLE) and from 0 to 8.3 % for Mohs micrographic surgery (MMS)

For recurrent and metastatic lesions, radiotherapy, chemotherapy and molecular target therapy with Imatinib mesylate should be considered as suitable alternative or additional treatment options[16].

The aim of this study is to compare the recurrence rate of the traditional surgical treatment with the recurrence rate of Mohs Tübingen technique (MTT), a surgical variant adopted for the treatment of DFSP that was developed in 1988 by Breuniger *et al.* at Tübingen's University in Germany and is particularly appropriate for large and deep excisions of skin cancers[27-29], allowing a three-dimensional visualization of the excision margins, the so-called "Tübingen Cake" (Fig. 1).

MATERIALS AND METHODS

Patients:

A retrospective review was conducted on 135 patients diagnosed, treated and followed-up for histologically confirmed DFSP at two institutions: SCDU Dermatology AOU Città della Salute e della Scienza, Turin (n=62) and SCDU Dermatology AOU Maggiore della Carità, Novara (n=73) between January 1997 and December 2014.

The records were analysed for gender, age at onset, tumour site, presentation, clinical variety, previous therapies, type of surgical treatment and surgical repair and relapse. The percentage of recurrences and onset of distant metastasis were evaluated and calculated for each treatment group, together to time to progression and follow-up.

Treatments:

The 62 patients treated in Turin underwent to wide local excision (WLE) and surgical margins were chosen based on the size of primary DFSP. If tumour site and anatomical structures allowed, a WLE including the underlying subcutaneous tissue and fascia was performed. Surgical margins were at least 2 cm of apparently healthy tissue for lesions of 2 or more cm in diameter, whereas were limited at 1.5 cm for lesions of less than 2 cm. Excision was limited also in patients in which lesions were located near critical structure such as face, scalp or on poor subcutaneous tissue anatomical areas. Grossly specimens were bread-loafed after inking of the resection margins. The border status was examined in multiple tissue sections taken perpendicular to the nearest margin with at least 1 section per cm. If any margins were microscopically involved, the lesions were further excised to obtain disease-free margins of at least one additional centimetre.

The 73 patients treated in Novara underwent to Mohs Tübingen technique (MTT). With MTT, the initial surgical margins were 5 mm, on clinically healthy skin. The specimen was oriented by affixing a wire that marks 12 o'clock relatively to the patient body axis. The tissue was sent for paraffin embedding to the Pathologist. Then, a thin circular strip of tissue from the margins and a slice from the bottom of the sample were cutted; the circular strip was divided into several parts depending on its size. Each part will be fixed, stained with H&E and systematically examined for the presence of the tumour. If any margins were positive, the lesions were re-excised in that exact point, to obtain disease-free margins without sacrificing healthy tissue. This operation was repeated until clear margins were obtained.

After surgery, wounds were repaired with direct suture, skin graft or flap, or else by secondary wound closure, to obtain the best cosmetic result.

In our case series, neo-adjuvant therapy with Imatinib mesylate was administered when surgical approach was primarily excluded because of tumour extension and risk of unacceptable aesthetic defects.

Data analysis and comparison with literature:

The data obtained about patients and treatments has been collected in a database, a descriptive statistic.

A comprehensive search of literature was performed using PubMed database. The following search criteria were used: ["Dermatofibrosarcoma, Protuberans"(Mesh)] and ["Mohs' Micrographic Surgery"(Mesh)] or ["Breuniger Technique"(Mesh)] or ["Standard Surgical resection"(Mesh)] or ["Wide Local Excision"(Mesh)]or ["Treatment"(Mesh)] or ["Review"(Mesh)]. The search was limited to English and French-language studies published between 1951 and 2015.

The following inclusion criteria (Table 1) were used to select original articles for analysis: retrospective review, case-control or cohort study designwith a number of patients greater than 10, treated in the same centre with a median follow-up period $\geq$ 5 years; treatments considered were SSR, WLE, MMS, MTT. Studies had to report sufficient information on relapses and follow-up, particularly on the median follow-up or extremes in order to calculate it. We reviewed the titles and abstracts of these articles and based on the inclusion criteria we identified those to be subjected to the full text review (Fig. 2). Then, we calculated and reported for the four considered treatment the annual recurrence risk rate, to compare them.

RESULTS

Clinical and histopathological features:

The characteristics of the study population are summarized in Table 2.

There were 62 males (46%) and 73 females (54%), with a median age at diagnosis of 46 years (7-86). DFSP developed on previously damaged skin in 7/135 cases (5.2%) and during pregnancy in two. The initial tumour size varies from 0.5 to 6.5 cm, with a median diameter of 3.5 cm.

The sites of primary lesions can be summarized as follows: DFSP were localized at trunk (including chest and abdomen) in 55 patients (40.7%), back in 31 (23%), arms in 18 (13.3%), legs in 19 (14.1%), head in 11 (8.1%) and genitalia in only 1 patient (0.8%).

The protruding form of DFSP was the most frequently observed clinical variety, occurring in 95% of cases (128 patients), whereas 5 patients presented morphea-like form and 2 congenital form. All DFSP were positive for CD34.

There were 122 primary (90.4%; 57 in WLE group and 65 in MTT group) and 13 non–primary tumours (9.6%; 5 in WLE and 8 in MTT group); from these 13 patients, 10 had undergone to one prior excision and 3 to two prior excisions.

Imatinib (Gleevec®) was administered at the dose of 400 mg/m^2 daily for nine months as neo-adjuvant treatment in 4 patients, allowing a significant decrease in the lesion size in all, with a subsequent complete surgical resection.

Surgical treatment:

Sixty-two out of 135 patients (45.9%) underwent to WLE whereas 73 (54.1%) to MTT. In WLE group, microscopically involved resection margins were documented in 3 (4.8%) out of 62 patients. In MTT group, surgical radicality has been obtained in one surgical time for 23 patients (31.5%) whereas for the remaining 50 patients (68.5%) 2 to 4 surgical steps have been necessary and in 17 patients fascia was excised.

Tumour size and site dictate reconstructive procedures: 73 patients (54.1%) underwent primary closure, 39 skin grafts (28.9%), 19 (14.1%) skin or myocutaneous flaps, 1 (0.7%) flap and graft, 2 (1.5%) closure by secondary intention and 1 (0.7%) primary and secondary wound closure.

Clinical course:

The recurrence rate after WLE was 8.1% (5 of 62 patients; all with primary tumour); instead recurrence rate after MTT was 5.5 (4 of 73 patients). From the 9 relapsed tumours, 3 were located on the trunk (33%), 3 on legs (33%), 2 on head (22%) and 1 on the back (12%). From the recurred patients treated with MTT, 2 (3.1%) had a primary and 2 (25%) a non-primary tumour. All relapses occurred as local recurrences.

All relapsed patients underwent to MTT and at the time of writing are disease free with a median survival >5 years (range 3-12 years).

After a median follow-up of more than 5 years, 130 of 135 patients (96.3%) were alive; 1 patients died for visceral metastasis from the primary DFSP lesion after 4.2 years from diagnosis and 4 died regardless of DFSP. Median follow-up time was 4.7 years in WLE and 9 years in MTT. Median time to relapse was 1.3 years (range 0.5-5.7) in WLE and 3 years (range 1-5) in MTT. These data are summarized in table 3.

Literature analysis:

The results of the literature review are reported in Tables 4-7. For SSR, 9 studies were considered, from 1967 to 2012. Sample size ranged from 13 to 66 patients, with a total of 253. Recurrences ranged from 0 and 25.8%, with a total of 28.5%. Median follow-up time was 8 years (2.8-13.2 years) and annual risk rate of recurrence was 3.6% (Table 4).

For WLE, 30 studies were retrieved, from 1951 to 2015. Sample size ranged from 10 to 218 patients, with a total of 1465. Recurrences ranged from 0 and 49%, with a total of 14,9%. Median follow-up time was 9.8 years (0.93-18.6 years) and annual risk rate of recurrence was 1.5% (Table 5).

For MMS, 16 studies were retrieved, from 1988 to 2014. Sample size ranged from 10 to 74 patients, with a total of 424. Recurrences ranged from 0 and 2.7%, with a total of 0.94%. Median follow-up time was 7.35 years (2.2-12.5 years) and annual risk rate of recurrence was 0.13% (Table 6).

Finally, for MTT 3 studies were retrieved, from 2007 to 2008. Sample size ranged from 10 to 41 patients, with a total of 82 and 0 recurrences. Median follow-up time was 4.2 years (3-5.4 years) and annual risk rate of recurrence was 0% (Table 7).

If we add to the studies about WLE our series of 62 patients, the total number of patients aggregate to 1527 and recurrences to 223, but median follow-up time and annual risk rate of recurrence remains unchanged.

For MTT we can add 42 patients of our series because 31 were included in the study of Gattoni et al.[30] (2007) reported in Table 7, for a total of 124 patients. Recurrences rising to 4 with a median follow-up time of 6.6 years (4.2-9 years) and an annual risk rate of recurrence of 0.5%.

DISCUSSION

This paper reports data about a wide series of patients affected by DFSP treated and followed-up at two different institutions. Epidemiological, clinical and pathological features of our patients agree with those of most series recently reported by the international literature.

The peak incidence of DFSP is commonly reported between 20 and 59 years[1,31-32]: in our experience, median age was 46 years. Most patients from our series presented lesions on trunk and back that are the most frequently reported location of DFSP[7,9,16,26,33-35].

The major incidence in females and the presence in our series of two cases developed during pregnancy could support the eventually hormonal origin of DFSP suggested by literature[17].

DFSP is commonly characterized by a low metastatic potential[20,36], even if the development of metastasis from DFSP is a poor prognostic sign and most patients die within 2 years from visceral involvement, despite chemotherapy administration. In our experience, visceral metastases were observed in only one patient, who died after 4.2 years from diagnosis. On the contrary, DFSP is known for its high tendency to recur locally after surgical excision, with a recurrence rate reported in literature up to 60%, depending on excision margins and surgical technique used[11,32,36,37].

To reduce the local recurrence rate, many authors recommend a wide local removal (never less than 2 cm in apparent healthy tissue) with histological confirmed free margins.

However, there is not a complete agreement about the distance from the tumour that guarantees its complete eradication and about the necessity of removing subcutaneous tissue and fascia. Moreover, the DFSP infiltrative growth pattern with tentacle-like extension makes frequent local recurrences also in presence of wide surgical margins[26,38].

In our experience the recurrence rate of DFSP is in accordance with literature data (8.1%) for patients treated with WLE, but this percentage is lower (5.5%) when we use MTT.

Indeed, Mohs surgery has been proposed by only a few authors as a useful alternative to traditional excision[39]. In MMS, the excised tissue is frozen and sectioned horizontally at 5-7 μm; position, orientation and staining of each specimen are drawn on paper (*Mohs' map)*. In this way, the Pathologist can report the exact location of any remaining tumour. By definition, Mohs technique should continue until all the surgical margins are microscopically clear, giving to the patient a high probability to be cured. MMS could spare a fair amount of uninvolved tissue, representing a possible surgical tool for body regions where wide excision is not feasible or cosmetically unacceptable. The recurrence rate reported for MMS varies from 0 to 8,3% and is significantly lower than WLE[5,25,30,38-61]. However, this kind of treatment is rather expensive and time consuming, particularly for large lesions like DFSP, where processing a high number of frozen sections is unfeasible. For this reason, MTT could represent an advantageous alternative, because all margins and deep side of the specimen are analysed at first cut, maintaining the possibility of sparing tissue and making easier to repair the surgical wound. Indeed, reconstructive surgery is very important in patients with wide lesions or DFSP located on head and neck or near critical anatomical structures.

Considering the high rate of recurrence described for DFSP, literature recommends a long period of follow-up in treated patients; particularly, Snow and Archontaki[53,62] suggest a follow-up longer than 5-years because many relapses occur after this period due to the sneaky behaviour of DFSP. Our data are conflicting with this affirmation; all our relapses occurred within 5-years from diagnosis. However, in our experience all relapsed patients showed more aggressive DFSP histotypes from the onset, and underwent to standard resection or Imatinib adjuvant therapy for histological persistence of DFSP without possibility of additional surgical treatment.

Our literature revision confirms that the most valid treatments for DFSP are represented by the two Mohs variant (MMS and MTT), showing an annual risk rate of recurrence of 0,13% and 0,5 % respectively, whereas SSR and WLE had a

higher annual risk of recurrence (3,6% and 1,5% respectively). These observations are confirmed by the comparison between recurrence rate reported in the papers on DFSP treatment in the past 15 years. The high recurrence rate of SSR (26%) makes this kind of treatment ineffective, whereas there are better guarantees for WLE, with a reported recurrence rate varying from 0 to 16%[62,63] Also the reported low recurrence rate of MMS[50,53,58,60,61,64-66] confirms its validity.
To the best of our knowledge, our study represents the largest series of DFSP patients treated with MTT, with the longer follow-up; so, we sustain the validity of our data, despite the discrepancies between our results and several literature reports. Moreover, when we take in account only the recurrence rate of primitive lesions, our rate drops to 3.1% similarly to that previously reported by Serra-Guillén[66] in 74 primitive lesions.

CONCLUSIONS

This study demonstrated that MTT could represent a good alternative to MMS in the treatment of primary DFSP. Moreover, histological analysis of the thick specimen with Tübingen-cake it is faster than MMS which requires several sections, further supporting the feasibility of this type of treatment.

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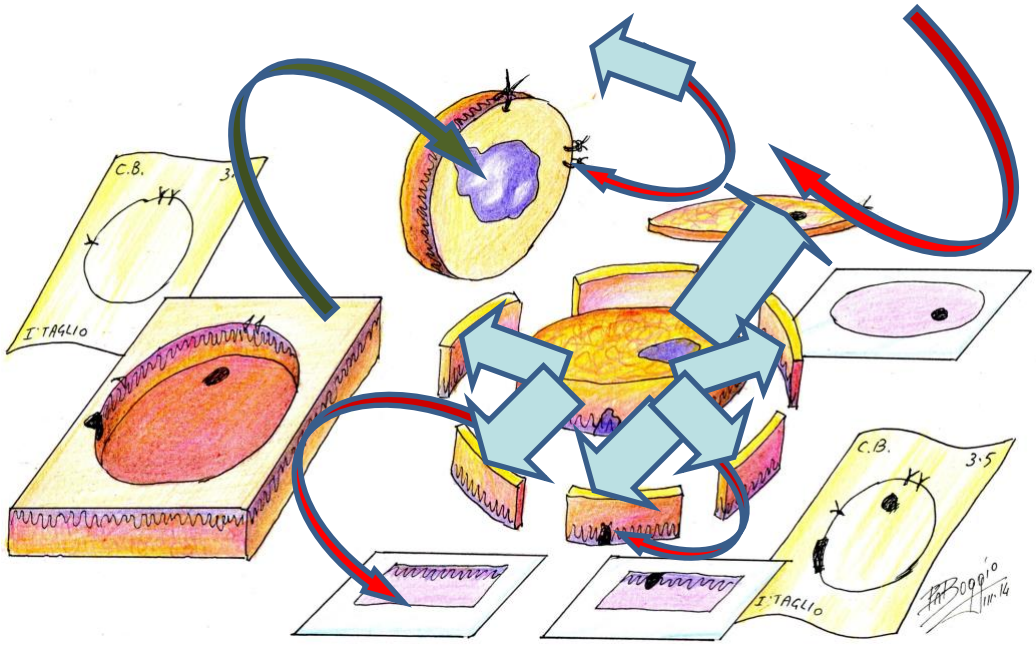

Fig. 1 "Tübingen Cake".

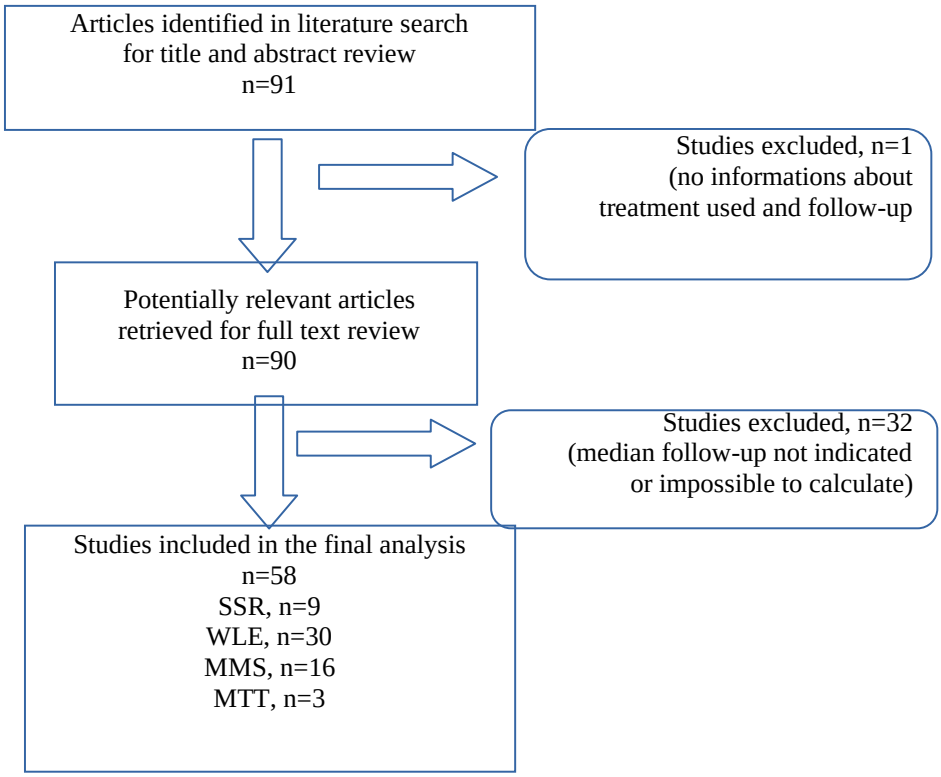

Fig. 2 Study selection flow diagram.

Inclusion criteria	Exclusion criteria
Retrospective review, case-control or cohort study design	Case report
> 10 patients	Case series
Same centre	Other treatments
Median follow-up ≥ 5 year	Lack of an appropriate control group
Treatments : SSR, WLE, MMS, MTT	Lack of informations of relapse or follow-up

Table 1. Inclusion and exclusion criteria of studies.

	No.
Sex:	
Male	62
Female	73
Median age at diagnosis (range)**:**	46 years (7-86)
Presentation:	
on apparently normal skin	128
on previously damaged skin	7
Site:	
trunk	55
back	31
arms	18
legs	19
head	11
genitalia	1
Clinical variety:	
protruding form	128
morphea-like form	5
congenital	2
Tumour:	
primary	122
non-primary (undergone to prior excision)	13
Surgical treatments:	
wide local excision (WLE)	62
mohs Tübingen technique (MTT)	73
Reconstruction:	
primary closure	73
skin grafts	39
skin or myocutaneous flaps	19
flap and graft	1
primary and secondary wound closure	3

Table 2. Characteristics of the study population.

Relapse:	
yes (WLE)	5
yes (MTT)	4
no	126
Site of relapse:	
trunk	3
legs	3
head	2
back	1

Median follow-up time:	
WLE	4,7 years
MTT	9 years
Median time to relapse:	
WLE	1,3 years
MTT	3 years

Table 3. Characteristics of relapse and follow-up in WLE and MTT groups.

Study, year	No of patients	No of local recurrences	Median Follow-up time (years)	Annual risk rate of recurrence
Longhin, 1967	44	14 (31,8%)	6	5,3%
Bendix-Hansen, 1983	19	8 (42,1%)	8,5	5%
Barnes, 1984	15	8 (53,4%)	12	4,4%
Rutgers, 1992	19	8 (42,1%)	13,2	3,2%
Mark, 1993	16	9 (56,25%)	9,5	6%
DuBay, 2004	40	0	4	0 %
Ruiz-Tovar, 2006	21	6 (28,6%)	2,8	10,2%
Monnier, 2006	66	17 (25,8%)	9,6	2,7%
Stivala, 2012	13	2 (15,4%)	5,2	3%
Total	**253**	**72 (28,5%)**	**8 (2,8-13,2)**	**3,6%**

Table 4. Summary information from studies about SSR.

Study, year	No of patients	No of local recurrences	Median Follow-up time (years)	Annual risk rate of recurrence
Pack-Tabah, 1951	39	8 (20,5%)	10,25	2%
Taylor-Helwig, 1962	98	48 (49%)	9	5,4%
McPeak, 1967	82	8 (9,8%)	9	1,1%
Tamoney, 1971	12	3 (25%)	15,5	1,6%
Waldermann, 1985	13	3 (23,1%)	4	5,8 %
Petoin, 1985	96	6 (6,25%)	8	0,8%
Chattopadhyay, 1986	10	6 (60%)	6	10%
Smola, 1991	20	6 (30%)	8,75	3,4%
Brabant, 1993	14	0	3,1	0%
Gloster, 1996	39	5 (12,8%)	3	4,3%
Arnaud, 1997	107	2 (1,9%)	5	0,4%
Hass, 1997	21	7 (33,3%)	5,5	6,1%
Bowne, 2000	159	34 (21,4%)	4,75	4,5%
Vandeweyer, 2002	18	1 (5,6%)	4,3	1,3%
Khatri, 2003	24	0	4,5	0%
Chang, 2004	60	10 (16,7%)	5	3,3%
Tan, 2004	10	0	6	0%
Fiore, 2005	218	8 (3,7%)	10	1,2%
Behbahani, 2005	34	0	5	0%
Popov, 2007	40	0	3,3	0%
Paradisi, 2008	38	5 (13,2%)	4,8	21%
Bague-Folpe, 2008	15	0	0,93	0%
Yu, 2008	18	0	5,7	0%
Edelweiss, 2010	13	7 (53,8%)	18,6	2,9%
Meguerditchian, 2010	28	1 (3,6%)	4,2	0,9%
Archontaki, 2010	16	0	3,6	0%
Erdem, 2011	120	38 (31,7%)	10,2	3,1%
Stivala, 2012	46	0	5,2	0%
Elamrani, 2014	32	8 (25%)	2,5	10%
Tan, 2015	25	4 (16%)	1,5	6,4%
Total	**1465**	**218 (14,9%)**	**9,8 (0,93-18,6)**	**1,5%**

Table 5. Summary information from studies about WLE.

Study, year	No of	No of local	Median Follow-up	Annual risk rate of

	patients	recurrences	time (years)	recurrence
Hobbs, 1988	10	0	3,6	0%
Gloster, 1996	15	1 (6,7%)	3,3	2%
Ah-Weng, 2002	21	0	4	0%
Nouri, 2002	20	0	4,7	0%
Sei, 2004	10	0	2,2	0%
Wacker, 2004	22	0	4,5	0%
DuBay, 2004	10	0	5,2	0%
Snow, 2004	29	0	12,5	0%
Hancox, 2008	25	0	8,4	0%
Nelson, 2008	44	0	3,3	0%
Meguerditchian, 2010	20	0	3,4	0%
Roh, 2010	11	0	2,2	0%
Tan, 2011	35	0	2,5	0%
Galimberti, 2012	11	0	3,7	0%
Loghdey, 2014	67	1 (1,5%)	4,2	0,4%
Serra-Guillen, 2014	74	2 (2,7%)	4,9	0,6%
Total	**424**	**4 (0,94%)**	**7,35 (2,2-12,5)**	**0,13%**

Table 6. Summary information from studies about MMS.

Study, year	No of patients	No of local recurrences	Median Follow-up time (years)	Annual risk rate of recurrence
Cecchi, 2007	10	0	4,2	0%
Gattoni, 2007	31	0	3	0%
Paradisi, 2008	41	0	5,4	0%
Totale	**82**	**0**	**4.2 aa**	**0%**

Table 7. Summary information from studies about MTT.