

## **EXTENSIVE CLINICAL EXPERIENCE: Changing Patterns in Diagnosis and Therapy of Acromegaly Over Two Decades**

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## **Abstract**

**Background:** The increased morbidity and mortality of acromegaly makes early diagnosis and therapy critical. However, whether the type of medical professional who first diagnoses acromegaly, the major complaint prompting medical attention, or the management paradigms utilized in the setting of novel medical therapies, have changed over time have not been well explored.

**Objective:** To identify the medical professional who first suspected acromegaly and the complaint prompting the diagnosis and if these have changed. Additional goals were to assess the interval from symptom onset to diagnosis of acromegaly and to compare treatment trends over consecutive decades.

**Design:** Case-record retrospective study.

**Setting:** Neuroendocrine Clinical Center at a tertiary care center.

**Subjects:** 100 patients (45 men and 55 women) with acromegaly referred from 1985-2005.

**Results:** Acral changes (24%) and headaches (20%) were most prevalent presenting symptoms prompting diagnosis. Eighteen % reported no symptoms of acromegaly at diagnosis. The primary care physician most often initiated the evaluation (44%). Comorbidities were more prevalent in older patients ( $p = 0.001$ ). The interval between symptom onset and diagnosis decreased, compared to previous reports. Radiation therapy was used less frequently in the decade after 1994 than in the prior (8 vs. 24%;  $p = 0.005$ ).

**Conclusions:** The primary care doctor plays the major role in diagnosis of acromegaly. Increased use of brain MRI may contribute to the many incidentally discovered cases and to the shortened time interval to diagnosis. Presumably due to availability of new medical therapies, use of radiation therapy has decreased.

## **Introduction**

Acromegaly is a rare disease, with an estimated incidence of 3-4 cases/million population/year and a prevalence of between 40-70 cases/million (1-6). In the majority of cases (95%), the cause is growth hormone (GH) hypersecretion from a pituitary adenoma. Although the mean age of disease occurrence is 32 years, the mean age at diagnosis is 39-42 years and most series report a delay in the diagnosis of 7-10 years from the onset of signs and symptoms (7). The mortality is 2-4 times higher than the general population and is predominantly due to vascular, metabolic and pulmonary co-morbidities (8-10). The mortality rate is directly related to the complications of GH excess, and normalization of growth hormone and/or IGF-1 secretion has been reported to reverse the increase in mortality as well as disease related morbidity (8,11-16). The clinical effects of GH excess may occur insidiously over many years and multi-organ complications are common (17,18). Tumor size and local tumor invasion are particularly relevant in acromegaly, as most studies report a higher proportion of macroadenomas (>65%) than microadenomas (18) and the prevalence of macroadenomas may partially reflect a delay in the time to diagnosis. Tumor size is an important predictor of surgical outcome and complications, with a reported 80-90 % cure rate in microadenomas compared to 50-60% in macroadenomas when surgery is performed by an experienced pituitary

neurosurgeon (19-24). Therefore, early recognition is considered key to achieving a high rate of treatment success (25, 26) and avoiding long-term co-morbidities.

Although the clinical manifestations of acromegaly have been extensively reported, there is limited information pertaining to the type of medical professional who makes the initial diagnosis of acromegaly and minimal data available regarding the initial complaint that prompts medical evaluation. In addition, many new medical therapies have become available over the past 20 years, including short acting and depot somatostatin analogs, cabergoline, and most recently, the growth hormone receptor antagonist. The impact of these advances on previously used treatment modalities, particularly the use of radiotherapy, is not well established.

## **Methods**

### *Patients*

Consecutive records ( N = 200) on patients with a diagnosis of acromegaly seen between 1985 and 2005 at the Neuroendocrine Clinical Center at Massachusetts General Hospital were selected for review. Patients were included (N =100) in the study if they had both a confirmed diagnosis of acromegaly and a complete medical record available. The diagnosis of acromegaly was based on clinical symptoms, presence of a pituitary adenoma on MRI scan, biochemical confirmation, including non-suppressed growth hormone on oral glucose tolerance test (OGTT) and/or normal IGF-1 concentration, and in surgically treated patients, a pathologically confirmed growth hormone secreting adenoma. The Partners Institutional Review Board approved the study.

### *Variables studied*

The history data was obtained on uniform collection sheets based on review of findings from the patient's complete MGH record as well as external records in patients who had prior evaluations at other centers. The interval between the time of onset of symptoms (based on patient report and prior medical records) and initial diagnosis (first record of elevated IGF-1 or GH testing) was determined. Tumors were characterized as incidentally found if the patient presented with no symptoms attributable to acromegaly at the time of diagnosis and thus by definition had zero years of delay in diagnosis. Other variables evaluated included patient demographics (sex, age at diagnosis), main complaint leading to diagnosis, type of professional seen, past medical history, size of tumor (micro or macroadenoma), therapeutic modalities used by referring or Center physicians, complications of therapy, IGF-1 level at diagnosis, co-morbidities at the time of diagnosis (as determined by the review of prior outside medical records as well as the history and physical exam recorded during the MGH Neuroendocrine Clinical Center visit) and therapeutic response (nadir suppression of growth hormone during OGTT and/or IGF-1 concentration). The 76 patients who had surgery at MGH were seen pre-operatively by a Neuroendocrine Clinical Center staff member. The 24 patients who did not have surgery at MGH were seen at different stages of their postoperative care (N =20) or were receiving primary medical therapy (N =4).

Remission was defined as normalization of IGF-1 levels and/or appropriate suppression of GH during an OGTT according to established criteria at the time of diagnosis (27-31). Patients were considered to have active disease if the IGF-1 concentration was above the age and sex adjusted normal range and/or GH did not suppress adequately during an OGTT at least three months after a primary form of therapy. These variables were also

compared between the two ten year periods (before and after 1995). Hypopituitarism was determined based on standard biochemical testing of pituitary function. Cortrosyn stimulation test or Insulin tolerance test (ITT) was used to assess adrenal insufficiency. A low free T4 with normal or low TSH was considered to be central hypothyroidism. Low testosterone and normal or low gonadotropins in men represented central hypogonadism. Low estradiol and low FSH in women with amenorrhea or menstrual irregularity was considered evidence of hypogonadism in women.

### *Statistical methods*

The data were analyzed using SAS software, version 8, from SAS Institute Inc., Cary, NC (USA). For statistical analysis of results, the chi-square test was used to compare proportions between groups. The Wilcoxon's rank sum test or Kruskal Wallis test was used depending on the number of groups being compared, to compare continuous measurement outcomes between the groups. All results were considered significant if two-sided  $p < 0.05$ . Data are expressed as mean  $\pm$  SD unless otherwise indicated.

## **Results**

### *Clinical and biochemical features*

Of the 100 patients, 55 were women and 45 were men. The mean age was  $41.2 \pm 14.2$  years, (range 10-80 years). The mean age at onset of symptoms leading to diagnosis was  $38.7 \pm 14.5$  years (range 8-78 years). The mean time to diagnosis was  $2.5 \pm 4.6$  years (median 1 year, range 0-32 years). Excluding patients who were diagnosed incidentally, the mean time to diagnosis was  $3.2 (\pm 5.0)$  years, (median 2 years, N = 82). To account

for changes in IGF-1 assays over the two decades, a mean IGF-1 factor was used (IGF-1/upper limit of normal (ULN) for assay) and at the time of diagnosis, was  $2.39 \pm 1.27$  (range 0.55-8.50). Eighty seven per cent of tumors were macroadenomas and 13% of tumors were microadenomas. Mean IGF-1 factor at diagnosis was  $2.4 \pm 1.2$  for microadenomas and  $2.4 \pm 1.3$  for macroadenomas. Twenty five per cent of patients were diagnosed before 1995 (Period 1) and 75% during or after that year (Period 2).

#### *Main complaint leading to diagnosis*

The most common problem leading to the diagnosis was acral changes (24%), followed by headaches (20%), amenorrhea (6% of total, 11% of women), dental changes (4%), carpal tunnel syndrome (4%), visual deficits (3%), sexual dysfunction (3%), arthralgias (2%), galactorrhea (2%), chest pain (2%), uncontrolled hypertension (2%), diabetes (1%), dizziness (1%), gynecomastia (1% of total, 2% of men), weakness (1%) and weight gain (1%). The most common initial complaint leading to diagnosis in both Periods 1 and 2 was acral changes followed by headaches (see Table 1). Four of the 100 patients with acromegaly had Multiple Endocrine Neoplasia 1 (MEN1). Among these patients, initial complaints leading to the diagnosis of acromegaly included galactorrhea (N = 1), dizziness (N = 1), chest pain (N = 1) and acral changes (N = 1).

Overall, acromegaly was incidentally diagnosed in 18 patients, 3 of whom had microadenomas and 15 macroadenomas. In these cases, patients were unaware of signs or symptoms of acromegaly prior to diagnosis and the diagnosis was made based on diagnoser's recognition of signs of acromegaly at an encounter in which the reason for the patient's being seen was unrelated to complaints clearly linked to acromegaly. Among the

18 patients diagnosed incidentally, 8 were diagnosed at a routine yearly medical visit (N = 6) and for continuing care visit (N = 2, one for high cholesterol and one for gastric polyps). Seven were recognized as a result of a radiographic finding, 6 on brain MRI and 1 on hand x-ray. Two of the brain MRIs were done for other CNS lesions (acoustic neuroma and schwannoma), 1 was part of a staging work-up for a testicular tumor and the other 3 were done for trauma evaluations. The hand film was done after a hand injury and the orthopedist suspected changes consistent with acromegaly. The other incidentally diagnosed cases were discovered in non-medical settings (N = 3). In all three cases physicians not involved in the patient's care observed the patients in a public setting and informed the patient of his/her concern about acromegaly. Overall 11/18 (61%) recalled symptoms once they were informed of the diagnosis and 15/18 (83%) had exam findings that were recognized at the time of diagnosis by the referring physician or by the neuroendocrine staff physicians. Seventy-two per cent of patients with incidentally found tumors vs. 39% of patients with symptomatic tumors had a co-morbid state (diabetes, hypertension, cardiovascular disease, or sleep apnea) when diagnosed ( $p = 0.02$ ). Comparing the two time periods, there was no significant difference in the number of patients with a diagnosis made incidentally, (4/25 prior to 1995 vs. 14/75 after 1995,  $p = 0.78$ ). However, all 6 of the patients diagnosed incidentally based on brain MRI were in the later decade, after 1994. Overall, 6/75 (8%) of patients diagnosed after 1994 versus 0/25 (0%) of patients before 1995 were diagnosed based on incidentally found brain MRI findings. In each period, the second most common reason to come to medical attention was an incidental finding rather than a medical complaint (see Table 1).

### *Medical professionals*

Table 2 shows the professional category of health care provider who first recognized acromegaly. The primary care physician initiated the evaluation of acromegaly in 44% of the cases, an endocrinologist in 13%, emergency room physician in 10%, neurologist in 6%, dentist in 3%, ophthalmologist in 3%. A pediatrician, urologist, Ear Nose and Throat (ENT) specialist and orthopedist each made the diagnosis in 2% of patients. An obstetrician/gynecologist made the diagnosis in 2 % of all patients and 3.6 % of women. A podiatrist, rheumatologist, cardiologist and pulmonologist each diagnosed 1% of patients. Seven per cent were self-referred for diagnosis. In the emergency room setting (N = 10), the reasons for seeking emergency care were headaches (60%, N = 6), head trauma (20%, N = 2) and cardiac disease (20%, N = 2). The primary care physician played a major role in the diagnosis of acromegaly in both periods (46% in Period 2 vs. 36% in Period 1;  $p = 0.25$ ; see Table 2). The order of frequency of professionals who first diagnosed acromegaly was comparable between the periods, although trends were found. The proportion of acromegaly cases diagnosed by an emergency room physician during the decade after 1995 (7%) was less than half that of the former decade (20%), (See Table 2). In addition, self-referred patients increased from 4% prior to 1985 to 8 % after 1985, including one self-referred through the Internet in the latter group.

### *Pre-existing morbidities*

Co-morbidities present at the time of diagnosis were diabetes mellitus (15%), hypertension (25%), coronary heart disease (5%) or sleep apnea (1%). Forty per cent of patients had multiple co-morbidities. Eight % of patients had a malignancy including papillary thyroid cancer (N = 3), breast cancer (N = 2), chronic lymphocytic leukemia (N

= 1) and prostate cancer (N = 1) and colon cancer (N = 1). More patients were diagnosed before than after age 40 (53% vs. 47%,  $p = 0.016$ ). The number of years of delay in diagnosis did not predict the presence of co-morbidities at the time of diagnosis in this population. Patients with one or more co-morbidities at the time of diagnosis, including diabetes, heart disease, hypertension or sleep apnea did not differ significantly in the number of years of delay in diagnosis compared to those who did not have these co-morbidities at the time of diagnosis (mean 2.1 +/- 3.9 years vs. 2.8 +/- 5.0 years,  $p = 0.25$ ). Patients with one or more co-morbidities at the time of diagnosis did not differ significantly in gender or mean IGF-1 factor compared to those who did not have these co-morbidities at the time of diagnosis. However, the age at diagnosis was predictive of the presence of a co-morbidity at the time of diagnosis, i.e., older patients were more likely to present with co-morbidities. The mean age at diagnosis was 48.0 +/- 14.8 years in those with a co-morbidity compared to 36.8 +/- 11.8 years in those with no co-morbidity, ( $p = < 0.001$ ). Seventy six and one half % of patients over age 55 at diagnosis had at least one co-morbidity compared to 32.5% of patients less than age 55, ( $p = < 0.001$ )

#### *Treatment modalities and outcomes*

Surgical treatment occurred at multiple surgical centers, as many patients were referred for endocrine management so that surgical outcomes represent results from many different surgeons. Forty six percent of patients had transsphenoidal surgery (TSS) alone, 28% had TSS + medical therapy, 12% had TSS + radiotherapy (XRT), 8% had TSS + XRT + medical therapy, and only 4% were treated with primary medical therapy. The

medications used included cabergoline, somatostatin analogs and pegvisomant and one or all more of these were used in 52 patients. The 4 patients treated with medical therapy alone were all receiving somatostatin analogs and all were controlled based on GH suppression tests and/ or IGF-1 levels in the normal range. One was receiving a combination somatostatin analog and pegvisomant. Among the 52 patients using medical therapy alone or medical therapy with surgery and /or XRT, 21 patients had normalized IGF-1 and or GH levels.

One percent had a craniotomy and 1% refused treatment. Surgical complications such as cerebral spinal fluid leak (N = 1), infection (N = 1) or bleeding (N = 1) were rare, occurring in 3.2 % of the 95 surgically treated patients. Overall, 51% of patients surgically treated at multiple surgical centers were cured. The preoperative mean IGF-1 factor was not significantly different between cured and not cured after surgery ( $2.29 \pm 1.39$  vs.  $2.50 \pm 1.1$  ( $\pm$ SD),  $p = 0.16$ ). Seventy per cent of patients with microadenomas and 48 % of those with macroadenomas were cured. The remaining patients had residual disease and required adjunctive treatment for control. Among all patients, including those treated with radiation, panhypopituitarism occurred in 11%, and transient diabetes insipidus in 3%. Women were more likely to have pituitary dysfunction ( $p = 0.0007$ ) with panhypopituitarism in 7 out of 11 and transient diabetes insipidus in 3 out of 3.

#### *Changes in Therapeutic Modalities over time*

The proportion of microadenomas and macroadenomas did not significantly differ between the two time periods (12 vs.13%, 87 vs. 88%;  $p = 0.86$ ). Trends in treatment modalities used changed during the periods. The overall use of TSS was similar during study periods before 1995 and after (96% vs. 93%). There was no significant difference in the use of TSS as the sole treatment (49%, N = 37) in Period 2 compared to Period 1

(36%, N = 9). However, radiation therapy was used much less frequently in Period 2 (8% in period 2, N = 6 vs. 24% in period 1, N = 6, p = 0.05), see Figure 1.

The proportion of patients cured compared to non-cured in the two time periods was not significantly different (56% vs. 49%; p = 0.64). The IGF-1 factor mean was not different among study periods  $2.43 \pm 1.67$  before 1995 and  $2.38 \pm 1.12$  after that time.

## **Discussion**

These results show a much shorter mean time to diagnosis (2.5 years) in those patients referred to this tertiary referral center compared to that previously reported in the literature. Even excluding incidentally found tumors, the mean time to diagnosis (3.2 years) is lower than previously reported. Three older series, including years from 1960 to 1983, reported a mean time of delay in diagnosis of 9.2, 6.6 and 10.2 years (1,2,7).

In our series, the most prevalent presenting complaints leading to diagnosis were acral change (24%) and headaches (20%). Most other series describe all disease-related clinical manifestations, rather than specifically reporting the presenting complaint prompting the diagnosis. Acral changes and headaches are among the most prevalent symptoms with a frequency up to 100% and 87% respectively (25). Thus it is expected that these symptoms were the most prevalent complaints leading to diagnosis.

In a series of 310 patients taken from Klijn et al and Nabarro, Molitch et al reported symptoms at presentation, including menstrual disturbances in 13%, acral changes in 11%, headaches in 8%, carpal tunnel syndrome in 6% and chance (detected by physicians, dentist or x-rays) in 40% (7,18,32). Despite the common finding of rheumatologic symptoms in acromegaly (33), this was a very uncommon (2%)

complaint leading to the diagnosis in this series. Of note, in the last decade, the second most common reason leading to the diagnosis of acromegaly was an incidental finding rather than a sign or symptom of the disease, and this may reflect the increased use of head MRI as part of the assessment of many types of complaints other than headache and routine use after head trauma. Most patients with an incidentally found tumor had a pre-existing disease unrelated to acromegaly which necessitated physician visits (74%) and this may have increased contact with a health professional and facilitated identification of acromegaly.

It is important to note that in this series, the diagnosis was most commonly suspected by the primary care physician (44%) which reinforces the critical role these professionals play in making this diagnosis. Few educational resources dealing with growth hormone excess are devoted to primary care and emergency room physicians although this study shows that these physicians play a major role in an early identification of acromegaly. These findings suggest that resources should be directed towards increased awareness of the disease and its diagnosis in this provider group. Self or relative referrals reflect an increased awareness regarding the disease by the general population during the last decade.

Co-morbidities in acromegaly have been well described (34-36). In their series, Jadresic et al reported a frequency of 34% for cardiac problems, 32% for hypertension and 27% for diabetes mellitus (35). In the large series by Ezzat et al 50% had hypertension and 30% had diabetes. A lower than expected proportion of the patients reported in this study

had diabetes mellitus (15%), hypertension (25%), or heart disease (5%). Cancer prevalence was also slightly lower in this study (8%) than in the prevalence rate reported based on collective prior series of 10.9% (34). The rate of papillary thyroid cancer at 3% is consistent with recent reports and supports a higher prevalence of thyroid cancer associated with acromegaly than expected in the general population (34), but ascertainment bias may contribute since these patients were more likely to be seen by physicians and specifically endocrinologists. While only a single patient had documented sleep apnea at presentation, this likely greatly underestimates the true presence of this condition as formal sleep tests were not routinely performed to detect this. The decreased morbidity associated with acromegaly in this cohort compared to previously reported series may reflect the shorter time to diagnosis reported in our series compared to others and supports the importance of early diagnosis in minimizing co-morbidities (34-36). The presence of any of these co-morbidities was not related to tumor size, presenting complaint, the type of professional making the diagnosis, or the time from onset of symptoms until diagnosis. Although the reported duration of disease did not predict co-morbidities, an older age at diagnosis was clearly associated with a higher rate of co-morbidity. Since older patients are more likely to have other diseases, age may be a confounder and causality between later diagnosis and higher morbidity cannot be established. Since most patients were diagnosed early in this cohort, the power to evaluate the impact of prolonged diagnostic delay on the development of co-morbidities was limited.

Transsphenoidal surgery is typically the primary therapy of acromegaly (16), and as such, was the most common form of therapy among our study population (94%). The surgical results reported here reflect the outcomes from multiple referring physicians across many centers where a dedicated pituitary surgeon may not have been available. Surgical cure rates reported from single centers, including our own, confirm that an experienced pituitary surgeon leads to increased surgical remission rates with fewer complications. (14,20,28,37-42). Radiation therapy was used less frequently after 1994. This decrease in the use of radiation likely reflects the greater availability of medical treatment options (43-49). Overall, almost 50% of women and 35% of men required medical therapy (octreotide analogs, dopamine agonists or a GH receptor antagonist) to control their disease after surgery.

In summary, analysis of records from a tertiary care referral center over two decades showed that the primary care provider and the emergency room physicians are key in identifying patients with acromegaly. In the last two decades, incidental findings, rather than symptoms of acromegaly, were the second most likely reason for the disease to be recognized and, in the latter decade only, brain MRI done for other reasons led to the discovery of many such cases. In recent practice, the time from the onset of disease to diagnosis of acromegaly is shorter than previously reported, likely related to improvements in diagnostic techniques and disease awareness. In this cohort, with an overall shorter time to diagnosis, the co-morbidity rate was also lower than in prior reports. Although the reported duration of disease did not predict co-morbidities, a later age at diagnosis was clearly associated with a higher rate of co-morbidity. Finally, in the

past decade, radiation therapy continues to be used but less commonly than in the preceding decade and this may be attributable to advances in pharmacological therapies for acromegaly.

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**Table 1. The Initial Complaint Prompting Assessment for Acromegaly and Adenoma Size at Diagnosis**

<b>Initial Complaint Leading to Diagnosis of Acromegaly</b>	<b>All Patients N=100</b>	<b>Period 1 N=25</b>	<b>Period 2 N=75</b>	<b>Presence of Microadenoma vs. Macroadenoma at Diagnosis</b>
Complaint	n	n	n	Tumor type
				<u>(Micro/Macro)</u>
Acral Changes	24	8(32)	16(21)	4/20
Incidental *	18	4(16)	14(19)	3/15
Headache	20	6(8)	14(19)	4/16
Amenorrhea	6	1(4)	5(6)	0/6
Dental	4	1(4)	3(4)	1/3
Carpal Tunnel	4	1(4)	3(4)	0/4
Visual	3	1(4)	2(3)	0/3
Sexual dysfunction	3	0(0)	3(4)	0/3
Galactorrhea	2	1(4)	1(1)	0/2
Arthralgia	2	0(0)	2(3)	0/2
Chest pain	2	0(0)	2(3)	0/2
Hypertensive crisis	2	1(4)	1(1)	0/2
Dizziness	1	0(0)	1(1)	0/1
Increase weight	1	0(0)	1(1)	0/1
Gynecomastia	1	0(0)	1(1)	0/1
Weakness	1	0(0)	1(1)	0/1
DM	5	1(0)	4(0)	1/4
Sleep apnea	1	0(0)	1(1)	0/1
<b>Total</b>	<b>100</b>	<b>25</b>	<b>75</b>	<b>13/87</b>

\*Incidental refers to a patient in whom acromegaly was diagnosed independently of symptoms related to acromegaly. The number in parenthesis is the percentage of the total in each in period.

Period 1 refers to those diagnosed in years 1985 to through 1994. Period 2 refers to those diagnosed 1995 through 2004.

**Table 2. The Type of Professional Who Diagnosed Acromegaly**

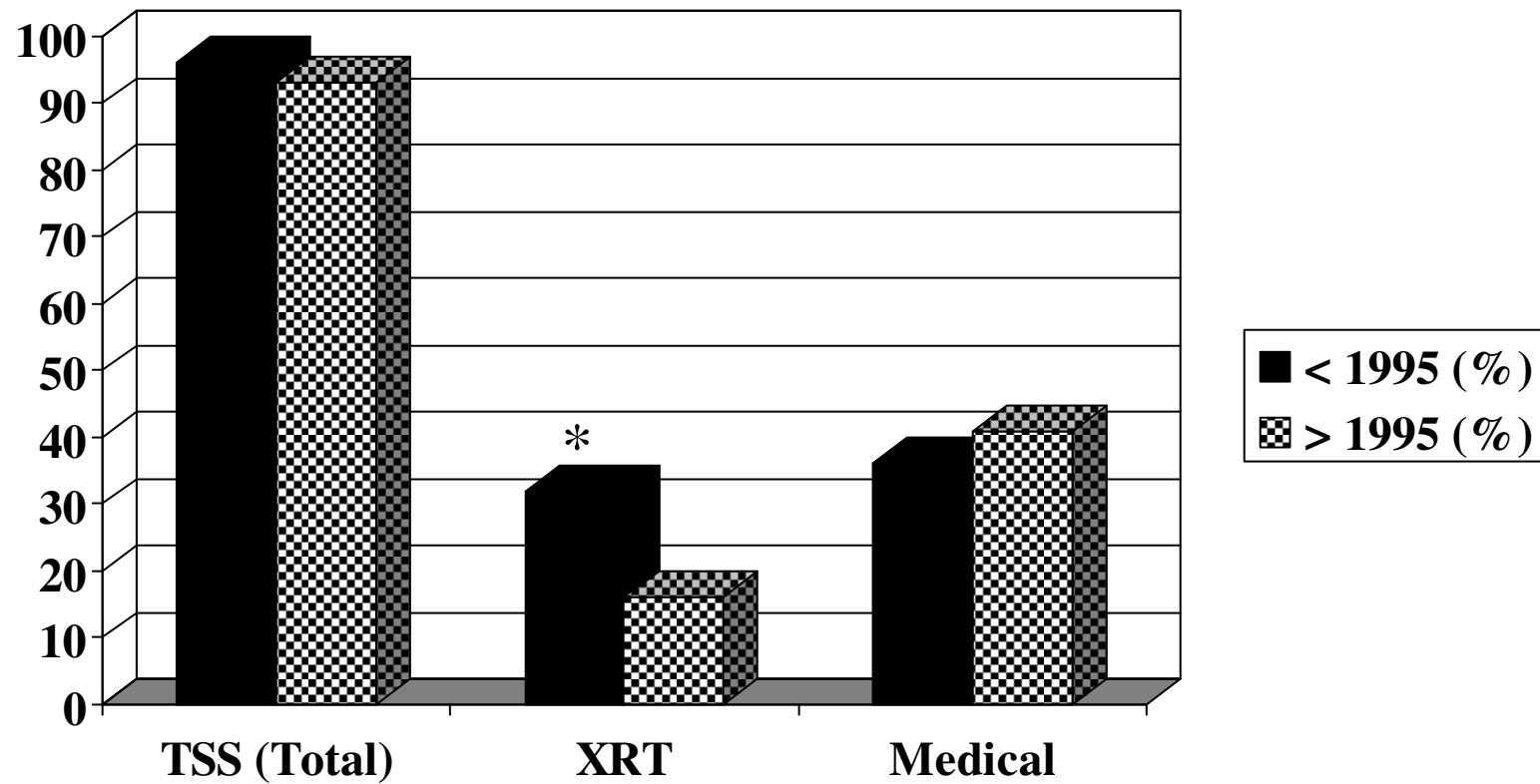
<b>1985-2004 N =100 Combined Periods</b>	<b>1985-1994 N =25 Period 1</b>	<b>1995-2004 N =75 Period 2</b>
<b>Primary Care</b> 44(44)	<b>Primary Care</b> 9(36)	<b>Primary Care</b> 35(47)
<b>Endo</b> 13(13)	<b>ER</b> 5(20)	<b>Endo</b> 10(13)
<b>ER</b> 10(10)	<b>Endo</b> 3(12)	<b>Neuro</b> 6(8)
<b>Self referred</b> 7(7)	<b>Self referred</b> 1(4)	<b>Self referred</b> 6(8)
<b>Neuro</b> 6(6)	<b>Dentist</b> 1(4)	<b>ER</b> 5(7)
<b>Dentist</b> 3(3)	<b>Ophtho</b> 1(4)	<b>Dentist</b> 2(3)
<b>Ophtho</b> 3(3)	<b>Neuro</b> 0(0)	<b>Ophtho</b> 2(3)
<b>Others **</b> 14(14)	<b>Others</b> 5(20)	<b>Others</b> 9(12)

\*\* Includes OB/GYN, ENT, Pediatrician, Urologist, Orthopedist, Rheumatologist, Cardiologist, Pulmonologist, Podiatrist,  $\leq 2\%$  for each for combined periods.

Neuro refers to neurologist; Endo refers to Endocrinologist; Ophtho refers to Ophthalmologist

N is total number of subjects in each category, number in parenthesis is % of total in each category

**Figure 1. Treatment Modalities**



\*P < 0.05

Patients 8/25 for < 1995 and 12/75 for > 1995.